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Mechanisms and Clinical Management

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The Lymphatic System and Cancer

Mechanisms and Clinical Management

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To Frances and Leslie Meyer
with admiration

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Preface

The constant threat of any cancer is of metastasis. As malignancies are diagnosed, critical questions quickly arise as to the extent of regional and systemic disease. To assess this, the status of the lymph node is by far our most commonly used guide, and the most frequently used basis for determining far-reaching oncologic decisions for therapy. But how well do we know the role of the lymphatic system in malignancy? To what extent does it effect a filtration or immune surveillance for the early control of carcinomas? Can we effectively encompass this captive disease or augment this surveillance by radical surgery, irradiation or pharmacological agents? What factors indicate that lymphatic involvement is a signal for inevitable systemic disease? For any cancer case, the answers given to these questions will often direct how radical the therapy will be, and often anticipate the difference between a cancer cure and failure.

New achievements in the *laboratory* analysis of lymphocyte and lymph node functions are contributing substantial insights into the activity of the lymphatic system in cancer, and bringing potentially sweeping implications for the management of cancer cases. New achievements in the functional and anatomical *diagnostic* evaluation of the lymphatic system are bringing equally important information about tumor involvement, and are providing new staging data for the management of our patients.

New conclusions from the *clinical* analysis of treated cases are quickly evolving within our oncology world of multi-institutional trials and computerized information dissemination. Valuable data regarding the role of the lymph node in directing therapy and in predicting therapeutic outcomes are coming forth as the focus of many protocol studies. The controversies about whether or not lymph node metastasis represents systemic disease can now be entered with

important new insights, often based on more complete understanding of the major prognostic factors involved.

The potential for lymph node involvement with cancer has often been used as argument in favor of radical therapies, especially the surgical removal of tumors in continuity with their lymphatic drainage tissues, or the equivalent wide-field treatment with irradiation. Therefore, many key issues regarding organ preservation hinge on the efficacy and need for lymphatic treatment, and are discussed in the immediately prior volume in this series, *Organ Conservation in Curative Cancer Treatment.* Important companion chapters may be found in that volume, especially regarding the management of cancers of the breast, as well as cancers of the head and neck, esophagus, bladder and prostate.

Ultimately, the questions regarding the role of the lymph node in the management of malignancies become as expansive as the field of oncology itself, and no single publication can document the full range of these concerns. In this volume, we focus on the primary controversies revolving around the assessment and management of lymphatic tumor involvement in common tumor sites. We are pleased to offer chapters contributed by authorities who are foremost in their fields.

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Lymph Nodes and Cancer

A Review

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Normal Structure of Lymph Nodes and Lymphatic Vessels

The lymphatic vessels of man – and other mammals – are present throughout the body with the exception of a few organs like the central nervous system and bones. These channels drain into regional lymph nodes, the majority of which are located near the axis of the body. The primary lymph channels reach the convexity of the lymph nodes (afferent lymphatics) and the secondary lymph channels leave from the hilus of the lymph nodes to connect with other nodes or with the thoracic duct (efferent lymphatics). The thoracic duct, which drains practically all lymph channels and nodes of the body, eventually empties into the left subclavian vein and thereby into the systemic circulation.

Not much is known about the structure of the lymphatic vessels, as compared with that of the blood capillaries. It is known however that it consists mainly of a continuous endothelial cell layer and that for the most part it does not have a basement membrane. Lymphatic channels possess valves that help in the motion of the lymph in the proper direction.

The lymph nodes (fig. 1) are bean-shaped structures varying from 1 mm to as much as 30 mm in maximum dimension. They are externally limited by a capsule made of collagen which encircles the organ and projects into the center by means of fibrous trabeculae that are arranged radially. Under the capsule is an interconnecting system of spaces called sinuses which are immediately below the capsule (subcapsular sinuses) or deep in the medulla (medullary

[1] The author is indebted to Dr. Robert Rouse for technical advice, Donna Buckley for editorial assistance, and Chris Morrow for collaboration in the artwork. Supported by Veterans Affairs research funds No. FAJ0004.

Table 1. Structure of human lymph nodes (see figure 1)

Cortex
(B-lymphocyte domain)
Primary follicles:
B lymphocytes, small
Some T lymphocytes
Dendritic reticulum cells
Secondary follicles:
Germinal centers
B lymphocytes (follicular center cells: large noncleaved, small and large cleaved)
Some T lymphocytes
Natural killer cells
Dendritic reticulum cells
Macrophages (often with 'tingible bodies')
Mantle
B lymphocytes, small
Some T lymphocytes
Dendritic reticulum cells

Paracortex
(T-lymphocyte domain)
T lymphocytes (mostly small)
Rare B lymphocytes
Interdigitating cells (Langerhans type)

Medulla (medullary cords)
(B-lineage domain)
B lymphocytes, small
Many plasma cells
Some T lymphocytes
Macrophages
Occasional mast cells, neutrophils, and eosinophils

Lymphatic vessels
Both afferent and efferent lymphatic channels are lined by a layer of endothelial cells arranged to form 'valves'
Small lymph channels lack a basement membrane
Large vessels have basement membrane and even a smooth muscle wall

Sinuses
Subcapsular: connected to afferent lymphatics; lined by (phagocytic) endothelial cells
Medullary: connected to subcapsular sinuses and efferent lymphatics; lined by macrophages
Cells in the lumina are mainly lymphocytes and macrophages

Blood vessels
Cortex and medulla supplied by arterioles, capillaries and veins, which enter and exit thru hilus
High endothelial (postcapillary) venules (site of entry of lymphocytes from systemic circulation) are located in the paracortex

Skeleton
The capsule and trabecula consist of mature collagen; reticulin fibers serve as support for the lymphopoietic cells; some nodes (e.g. iliac) have thick collagen bands criss-crossing cortex and medulla; others (e.g. axillary) have a shell-like shape, arranged around a spheroidal mass of mature adipose tissue

sinuses). The former are lined by endothelial cells while in the latter the endothelium is replaced by macrophages. The medullary sinuses for the most part are oriented radially and are connected with the subcapsular sinuses.

Surrounded by the aforementioned supporting structures is the lymphoid tissue (fig. 1, table 1). It consists of cortex, paracortex, and medullary cords. The

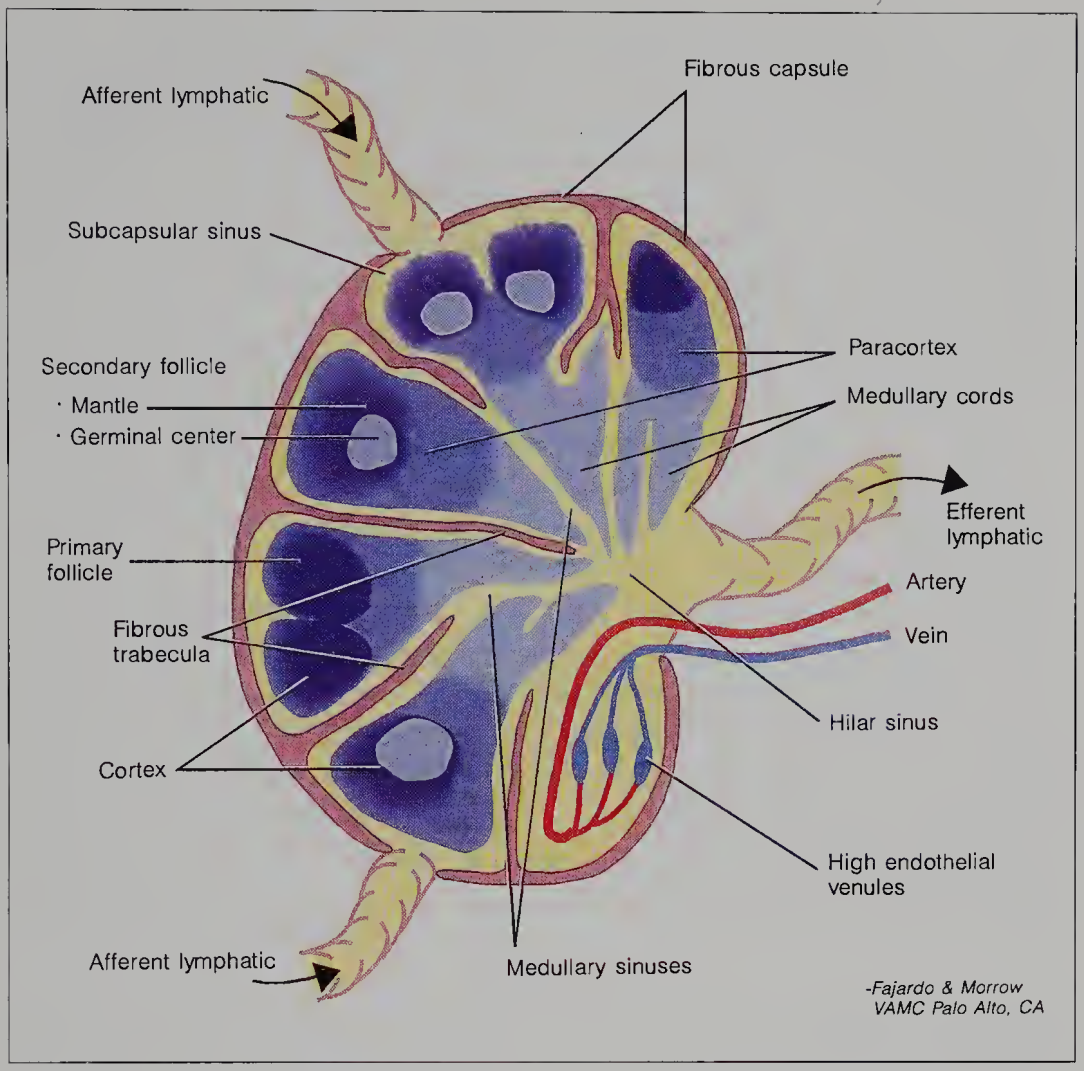

Fig. 1. Structure of a normal human lymph node (see text and table 1 for details).

cortex, located immediately adjacent to the subcapsular sinuses, is made of units called primary follicles which are B-cell domains. These follicles, when stimulated, develop germinal centers and become secondary follicles. The germinal center is a conglomeration of proliferating lymphocytes (so-called centroblasts or follicular center cells) which are especially prominent in young germinal centers. It also has nonproliferating B lymphocytes, antigen presenting cells called dendritic reticular cells (DRC), macrophages, and T lymphocytes. Around the germinal center is a layer of tightly apposed lymphocytes often showing 'onion skin' arrangement. This is the mantle and contains also B lymphocytes. In histologic sections the mantle usually covers eccentrically the germinal center, with the thicker zone often oriented toward the capsule.

Around the mantle is a dense cellular mass called the paracortex. There is usually no sharp delineation between paracortex and cortex and even less between paracortex and medullary cords. However, by immunohistochemistry it is easy to demonstrate that the majority of the cells in the paracortex are T lymphocytes, i.e. the paracortex is a T-cell domain. In addition to the T lymphocytes the paracortex contains antigen presenting cells, similar to the Langerhans' cells of the dermis, called interdigitating cells (IDC). Towards the center of the lymph node, i.e. central to the paracortex and among the medullary sinuses, are the medullary cords. These cords are composed of mature B cells, i.e. plasma cells, and some small lymphocytes [1, 2]. Thus, the medulla and areas of the paracortex are in close relation to the medullary sinuses which are lined by macrophages.

Functionally the cortex is a zone of proliferation of B cells that develops upon antigen presentation by DRC, and also contains memory B cells. The medullary cords are the main sites of antibody production, by plasma cells. In the paracortex T cells are stimulated by the antigens presented by the IDC, and memory T cells are generated. Phagocytosis occurs not only in the medullary sinus, but also in the cortex and paracortex [1, 2].

To recapitulate the circulation: the afferent lymphatics, i.e. those draining into the lymph node, penetrate through the capsule in the convexity of the node and empty into the subcapsular sinuses. These sinuses in turn connect with the medullary sinuses, draining into the efferent lymphatic which leaves the lymph node from the hilar area [1, 2]. The blood vessels of the node enter and exit through the hilus. Important for the entry of lymphocytes from the blood stream are the high endothelial venules (HEV) located in the paracortex.

Alterations in Lymph Nodes Draining Neoplasms

Multiple changes have been described, in humans and in other animals, in the regional lymph nodes draining a malignant tumor. These are morphologic and functional.

Structural Changes

In general, lymph nodes draining a malignant tumor show expansion of both the B and T domains [3], i.e. there is expansion of the cortex and paracortex. Often there is follicular hyperplasia. This hyperplasia has been judged by some investigators to be a favorable sign for the patient. Another type of reaction to a local neoplasm is marked increase in the macrophages within the sinuses, particularly the medullary sinuses. This is called sinus histiocytosis and also has been claimed to be a favorable sign. Both of these are nonspecific changes, seen in many different conditions; furthermore, they do not occur in all of the lymph nodes dissected in radical operations for malignant tumors although are observed quite frequently. Of course the most characteristic and ominous alteration is the presence of metastasis (see below).

Functional Changes

To understand these alterations it is important to be familiar with the normal functions of the lymph nodes in relation to tumors.

First there are mechanical functions which involve the lymphatic vessels and the lymph nodes. The lymphatic vessels provide channels for dissemination of tumor cells into lymph nodes and eventually into the systemic circulation. Also the lymph nodes provide a filter function which, as described in 'Metastases' below, is not very efficient [4–6]. For instance, carbon particles 150 nm in diameter were sequestered less efficiently (69% of nodes) by regional lymph nodes with metastases, than by lymph nodes without metastases (76%) in 10 patients with gastric cancer [5].

In addition to these functions the lymph nodes react to tumors by activating the immune system [1]. This implies the recognition of tumor cell antigens with the presentation of such antigens to the appropriate B and T cells (which initiate the adaptive immune response), and the natural immune response [1]. The latter requires no prior sensitization and is nonspecific. It involves macrophages, neutrophilic granulocytes and natural killer cells (NKC – mostly granular lymphocytes). Although NKC are normally present only in small numbers in the lymph nodes, activated nodes show a significant increase in NKC [1, 3].

The adaptive immune response to the neoplasm involves antigen presenting cells which must possess major histocompatibility complex (MHC I or II),

and stimulation of T cells. Activated T cells produce tumor inhibition or tumor lysis, and cytokines. The cytokines include migration inhibition factor, macrophage activation factor, macrophage chemotactic factor, lymphotoxin, tumor necrosis factor α, transferring factor, interferons, transforming growth factor β, etc. These cytokines activate other T cells as well as NKC. In this process memory cells are created [1, 7]. There is also evidence [8] that lymph nodes in the vicinity of malignant tumors (e.g. melanomas), have suppressor T cells which actually antagonize the antineoplastic immune response.

Activation of B cells directly by the antigen (if they possess Ig receptors) or by the antigen presenting cells mentioned above will result in production of antibodies which respond to the tumor cells' surface antigens. This antibody response is of variable effectiveness [1]. In most tumors it is only a response to nonspecific antigens and therefore the antibodies are nonspecific and inadequate or subadequate. In a few tumors which are very antigenic, the surface antigens are specific and the response may be effective in the control of such tumor cells. Experimentally the production of very specific antibodies against tumors can be obtained by prior immunization of the host with tumor antigens which are named tumor-associated transplant antigens. These are rather effective, but the model is purely experimental. In several human tumors there are other antigens characteristic but not totally specific of the tumor because they are also found in embryos or fetuses. Examples of these 'retrogenetic' antigens are the α-fetoprotein (α-FP) and the carcinoembryonic antigen (CEA) [1].

Characteristics of Lymphocytes in Regional Lymph Nodes (RLN) Draining Tumors

In vitro studies of the individual lymphocytes composing the RLN have shown that, as compared with blood lymphocytes, the RLN lymphocytes are less responsive to autologous tumor cells when they are co-cultured, and generate less cytolytic T cells [3, 9]. Also the B cells of the RLN generally do not generate in vitro tumor-specific monoclonal antibodies [3]. In fact the RLN lymphocytes respond often to irrelevant tumor antigens, while the blood lymphocytes do respond to relevant tumor antigens [10]. The RLN respond less to polyclonal mitogens such as phytohemagglutinin (PHA) [3]. In the RLN, as is the case in the normal lymph nodes, the natural killer cells are few. However, NKC can be increased in vitro by preincubation with some cytokines [3].

Tumor-Associated Immunosuppression

It is important to realize that in addition to the native deficiencies listed above, and to the tumor-induced alterations of the RLN just mentioned, there is often a generalized tumor-induced immunosuppression which is expressed

by a tendency to develop certain infections. Furthermore, many patients are treated by chemotherapy, and this affects both B and T lymphocytes. As described elsewhere, radiation also alters the immune response.

Immunosurveillance

For many years it has been postulated that the immune system has a 'vigilance' function designed to detect the early stages of development of neoplasms and to mount an immune response against these tumors. Although tumor immunosurveillance has not been proven, least of all in humans, it may exist and in fact may be responsible for the absence of tumors in many individuals. If so, it may be effective either during the oncogenesis period or after the development of the tumor [1]. It would have a complex mechanism, involving T cells, NKC, probably macrophages and neutrophils [1] and it may even involve humoral immunity.

The concept of immunosurveillance also has to include the concept of mechanism(s) through which some tumors escape the surveillance, in order to explain the development of neoplasms; this is called 'immunological escape' [1]. It is likely that some tumor cells are capable of escaping such an immune surveillance, and in fact it has been suggested that a small number of tumor cells is more efficient in producing metastasis than massive numbers which could trigger a massive immune response. Other mechanisms of escape include the following: antigen 'modulation' from the surface of the T cells; antigen masking; antigen tolerance; lymphocyte trapping (e.g. in RLN) with 'tolerization'; genetic differences (e.g. in the MHC haplotype); blocking antibodies forming antigen-antibody complexes which impair the response; tumor products, for instance prostaglandins, which also could impair response, and lack or alteration of factors and cytokines such as interleukins-1 and -2 which are needed for the amplification of the immune response [1].

Summary of the Role of RLN in Cancers

In the early stage of neoplasia, RLN may have an important anti-tumor function [3]. This has not yet been proven in humans [3]. In the later stages of tumor development, with progressive growth, the RLN probably are not adequate to mount anticancer defenses [3]. Furthermore, RLN actually may provide a good environment for the growth of the tumor [8] and its dissemination, as will be described below.

Metastases to Lymph Nodes

Generalities about Metastases

For each malignant neoplasm, only some, if any, subpopulations of cells express a metastatic phenotype, i.e. only some subgroups of cells are capable of metastasizing [11]. Rapidly growing tumors shed many cells into the circulation: thousands to millions of cells per day for tumors measuring about 1 cm in diameter [6]. However, only less than 0.01% of such cells are actually capable of initiating metastatic colonies [6], and these colonies do not necessarily progress into growing tumors. In addition, metastases larger than approximately 500 μm (0.5 mm) in diameter require microvessels (angiogenic response) for survival and growth [12].

The Metastatic Cascade

Several steps are recognized in the process of dissemination of tumor cells from the primary tumor to distant sites [6]. The tumor cells must attach to their basement membrane (BM), e.g. by laminin receptors in tumor cells. Tumor cells so attached must produce enzymatic degradation of the BM, by means of metalloproteinases such as collagenases IV and V, heparinases, cathepsin, etc. [6].

Having penetrated the BM the tumor cells must move through the surrounding stroma, and this is accomplished by means of chemotactic and chemokinetic cytokines such as the autocrine motility factor [6]. Pseudopodia are necessary for the migration of these cells. This migration may carry the cells to structures like a blood capillary, where they in turn have to penetrate its BM and migrate through the endothelial cells into the lumen.

Metastatic Steps from Primary Tumors into RLN

There is limited information about the intimate mechanisms of lymph node metastases [4]. However, based on the data available for hematogenous spread of neoplasms, the following data can be applied by analogy to lymphatic spread. Several steps must be accomplished by the tumor cells in order to reach the lymph node and beyond [6, 11, 13, 14].

Invasion: Once the T cells have recognized – and attached to – the BM (e.g. by laminin receptors), the next step is to penetrate it, i.e. to become invasive. This involves many metabolic and genetic changes. One of them may be the down-regulation of normal adhesion molecules (cadherins) recently reviewed [15]. Then there is enzymatic degradation of the tumor BM; this is accomplished by means of the already mentioned metalloproteinases (collagenases IV and V), as well as cathepsins, heparinases etc.

Locomotion: The cells migrate through the degraded BM and into the matrix using their pseudopodia and directed by chemotactic cytokines and by

chemokinetic substances. The autocrine motility factor is among the best known of these substances [6].

Attachment to the stromal matrix: This is accomplished by means of molecules such as integrins that recognize collagens, fibronectin, vitronectin, etc. [15].

Enzymatic degradation of the stromal matrix: The tumor cell uses collagenases (I, II, III) to digest the stromal matrix, cathepsins, heparinases, and plasminogen activator [6].

Locomotion through the matrix: This will continue by repetition of the previous steps and with the help of the pseudopodia. Since most malignant (and benign) neoplasms do not contain lymphatic vessels, the tumor cells must migrate to the periphery of the neoplasm to reach the lymphatic vessels of the host.

Penetration into lymphatic vessels: Because lymphatic capillaries lack a BM [2], tumor cells penetrate their wall either by separation of the endothelial cells or by invagination into endothelial cells, and finally reach the lumen [4, 13].

Intralymphatic flow: Within the lymphatic vessels, cells follow the flow of lymph arriving into the afferent lymphatic and through it into the subcapsular sinus of the lymph node. It is not clear whether host cells – such as macrophages – may be necessary for this transit.

Arrest: For unknown reasons (adhesion of tumor cell integrins to lymph node vitronectin?) [16] tumor cells are often arrested in the subcapsular sinus and are often capable of proliferating in this location to form a colony [4], which is a familiar sight to pathologists.

Growth in lymph node: Once in the subcapsular sinus, tumor cells either may be contained within the node or may migrate from it. If they are contained there are, again, various possible outcomes: the tumor cells may be destroyed locally, or they may invade, focally or extensively (sometimes replacing the entire node). Extracapsular extension of lymph node metastasis is an ominous sign that correlates with recurrence, particularly in the nodes of the neck [17, 18], and poor survival [19]. Probably in many instances tumor cells do not remain in the node but migrate from the primary colony into the medullary sinus and exit through the efferent lymphatic. Experimental studies have shown that within 10–60 min of the arrest of tumor cells arriving into the subcapsular sinus, exit of tumor cells can occur through the efferent lymphatic [6]. Metastases from carcinomas tend to appear first in the subcapsular sinuses as expected. Certain tumors, like melanomas, have a sinusoidal pattern of invasion. Carcinomas very often, and predominantly, metastasize initially to lymph nodes; other tumors (many sarcomas) may bypass RLN or metastasize by hematogenous dissemination into the lung, or other sites.

Conclusions

The anatomy of the regional lymph nodes and their multiple immune functions are deeply disturbed by the malignant neoplasm(s) they drain. Whether these alterations prevent tumor dissemination in most cases, or not, is unclear. In the early stages of neoplasia RLN may have an important antitumor function which, so far, has not been proven in humans. Later on, with progressive growth, the regional nodes probably are not beneficial; their local anticancer defenses are inadequate [3]. Actually, RLN may provide a good environment for growth and dissemination of the tumor: as noted, lymph nodes are poor mechanical barriers for the containment of a tumor that has metastasized into them.

The clinical importance of lymphatic metastases was well summarized by Heys and Eremin [3] recently: 'Involvement of regional lymph nodes by tumor cells is a prognostic index of survival and a biologic indicator of more distant metastatic disease. In most solid tumors in humans, removing the draining lymph nodes seems to have little impact on survival although it may be important in local control of disease.'

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Tumor Microenvironment: Paracrine and Autocrine Growth Mechanisms and Metastasis to Specific Sites[1]

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Paget [1] suggested that certain cancers spread nonrandomly to particular secondary sites on the basis of unique tumor and host properties. In such cancers, metastatic colonization of particular sites cannot be explained by mechanical considerations, such as the lymphatic or circulatory linkage of the secondary site to the primary tumor or the configuration of the lymphatic or circulatory system. It is now well known that mechanical and anatomical considerations, such as mechanical lodgment of tumor cell emboli in the first capillary bed encountered, are important factors in lymphatic and blood-borne tumor spread. However, after observing the unique patterns of colonization of breast cancers and microorganisms, Paget [1] proposed that metastatic development was not based solely on mechanical and anatomical considerations, but was a consequence of particular tumor cells ('seeds') finding a suitable environment ('soil') in which to develop and grow. In lymphatic tumor spread, however, tumor cells shed into the lymph commonly lodge in the first lymph node encountered. Although tumor cells can occasionally 'skip' a node and lodge in a subsequent node, the first lymph node encountered is usually the first site of metastatic colonization.

Both normal and malignant cells may produce a variety of substances – many are well-investigated – that specifically affect surrounding cells of the same type (autocrine factors) or cells of different type (paracrine factors). These

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Table 1. Tumor cell and host properties associated with the site preference of metastasis

Tumor cell properties

Cancer cells that have the property to metastasize nonrandomly to certain sites, particularly distant metastatic sites, are able to:

(a) Adhere to the microvascular endothelial cells of the target organ [4–6]
(b) Respond to chemotactic signals released from the target organ cells [7, 8]
(c) Invade and degrade the subendothelial matrix of the target organ [9, 10]
(d) Evade the immune surveillance systems of the target organ [11, 12]
(e) Respond to local soluble and insoluble growth signals in the target organ [13–15]

Host (organ site) properties

For metastatic colonization to be successful, the organ site must possess the appropriate type of:

(a) Microvessel endothelial cells [16, 17]
(b) Organ matrix or stroma [5, 18]
(c) Paracrine motility factors [7]
(d) Paracrine growth factors [13–15]

may critically influence tumor deposition and growth in lymphatic tissues as well as other organs. Some of the tumor cell ('seed') and host ('soil') properties associated with the site preference of metastasis, as well as their roles, have been identified [2, 3] and are listed in table 1. The interaction of the tumor cells with the appropriate organ effector cells may also be important at both the primary and secondary sites [19, 20].

As cancer cells undergo malignant progression and metastasize to regional (lymph node) and distant sites, they also undergo changes in their biologic properties. At the initial stages of metastasis, many cancers show what is called organ or site specificity, a tendency to metastasize to specific sites [3]. However, although there is a preference of metastatic cells for colonizing certain sites, it is never entirely site-specific [2, 3]. In terms of their growth properties, metastatic cancer cells that colonize distant sites should be less dependent on their usual tissue growth factors and inhibitors and more growth responsive to cytokines in new secondary microenvironments, such as lymph nodes and distant organ tissues [21].

Growth Properties of Cancer Cells

The responsiveness of cancer cells to paracrine growth factors, which may be expressed differentially at particular metastatic sites, could explain why certain cancers show a site preference for metastatic growth [3, 21]. It could also explain the increased numbers of affinities of particular growth factor receptors

and enhanced responses to the growth factors shown by such cancer cells. Overexpression of the c-*erb*B-1-encoded epidermal growth factor (EGF) receptor is associated with poor prognosis or enhanced metastasis in breast carcinomas [22]. A related gene, c-*erb*B-2/*neu*, encodes the cell surface receptor p185 (a reputed growth factor receptor); overexpression of p185 is associated with poor prognosis in breast [23] and ovarian carcinomas [24]. The EGF and p185 receptors can form a bimolecular complex [25], and overexpression of one or both of these receptors can result in mitogenic signaling. There are other examples of alterations in growth factor receptors during progression of cancer to more malignant states; the growth factor receptors that are overexpressed are probably the ones that are important in metastasis [21].

To demonstrate that the overexpression of growth factor receptors is important in tumor progression and metastasis, gene transfer has been used. Changes in metastatic properties and enhanced growth potential of cells transfected with the growth factor receptor gene usually (but not always) occur after gene transfer. For example, changes in metastatic properties of the c-*erb*B-2/*neu*-transfected NIH 3T3 cells occurred concomitantly with increased adhesion to microvessel endothelial cells, increased invasiveness through a reconstituted basement membrane, and increased cell motility in response to organ chemotactic factors [26]. Not all of the transfected cells, however, were converted to the metastatic phenotype [27]. In another study, a mutated c-H-*ras* oncogene converted papillary transitional cell carcinoma cells of the bladder to a more invasive phenotype and increased the cell surface expression of EGF receptors [28]. The enhanced expression of EGF receptors was thought to be partially responsible for the increased malignancy.

Paracrine growth factors and inhibitors are important in determining the growth potentials of metastases at various organ and tissue sites. Cancers are often dependent, at least at their initial stages, on paracrine growth factors released from surrounding host cells [21]. However, once progression to the metastatic phenotype occurs, growth is often modified in response to growth factors and inhibitors expressed at secondary sites [21].

Animal models have been useful in demonstrating that the site preference of metastasis is correlated with enhanced mitogenic response to growth factors and inhibitors expressed at secondary sites [13–15]. Several investigators have found that the growth of metastatic cells is stimulated when treated with medium conditioned with tissues derived from the organs at risk for metastatic colonization [13–15]. For example, Chackal-Roy et al. [29] found that bone marrow-derived medium contained a growth factor that stimulated the growth of bone-metastasizing prostatic carcinoma cells. Not all investigators, however, have found a close relationship between organ preference of metastasis and growth in target organ tissue-conditioned medium [30].

Transferrin-Like Factor as an Important Mitogen in Organ Tissue-Conditioned Medium

Several investigators have identified cell-derived mitogenic substances in medium conditioned with organ tissue [13–15]. Szanuiawska et al. [31] and Yamori et al. [32] found that lung tissue-conditioned medium contained both growth-stimulatory and growth-inhibitory molecules, which were crudely separated by gel filtration. The major lung tissue-derived growth factor for a variety of metastatic cells was purified from conditioned medium [33] and found to be a transferrin (Tf) [34]. This molecule was the first growth factor purified on the basis of its ability to differentially stimulate the growth of cells highly metastatic to a particular organ site. Tf probably acts as a paracrine growth stimulator in other organ sites as well. For example, Rossi and Zetter [35] found that Tf is a major growth factor for prostate cells that are metastatic to bone.

Because we had identified the major mitogen from tissue-conditioned medium as a Tf molecule, we examined the ^{125}I-Tf binding properties and growth response to Tf of tumor cell sublines with different metastatic properties. Using murine melanoma and rat mammary adenocarcinoma metastatic systems and a human breast cancer system metastatic in the nude mouse, we found a close relationship between binding of ^{125}I-Tf, growth response to Tf, and spontaneous metastatic potential [36–38]. The highly brain-metastasizing sublines showed the highest binding of ^{125}I-Tf, followed by the highly, intermediately, and poorly lung-metastasizing line, in that order. Using human MCF-7 breast cancer cell lines selected for loss of hormone responsiveness and for invasive abilities in nude mice, we also found by analyzing Scatchard plots that the more invasive and metastatic lines bound more of ^{125}I-Tf molecules [38].

When we treated lung tissue-conditioned medium with control biotinylated goat anti-Tf and streptavidin-agarose, there was a significant reduction in the growth potential of the medium. We therefore demonstrated that Tf or Tf-like activity in the medium was responsible, in part, for the stimulation of tumor cell growth [37]. Although the functions of paracrine growth factors are unknown, they might be involved in controlling proliferation of certain cells during wounding and inflammation processes [21]. Overexpression of particular growth factor receptors may be important in metastatic cell growth response at certain sites or at sites of wounding or inflammation. Thus, tumor cells that express high numbers of Tf receptors should be able to respond to low, limiting concentrations of Tf that exist in some tissue compartments, such as the brain, where Tf is active as a paracrine growth factor during fetal development [39].

Extracellular Matrix-Bound Growth Factors and Metastatic Colonization

In addition to soluble growth factors, molecules from the tissue extracellular matrix and basement membranes can stimulate tumor growth. Extracellular matrices and basement membranes contain some tightly bound growth factors [40]. In addition, other molecules derived from extracellular matrix may modulate growth and differentiation, such as laminin and heparan sulfate proteoglycan [41]. Extracellular matrices isolated from different organs appear to have differential growth-modulating effects on metastatic cells that show site preference. For example, Deorr et al. [42] found that extracellular matrix prepared from various organs did not equivalently stimulate the growth of metastatic rat mammary carcinoma and human hepatoma cells. Only the highly metastatic cells were differentially stimulated to grow at clonal densities by matrix from the target organ for metastasis formation. The glycosaminoglycan fraction from target organs was the most active growth regulator [42].

Paracrine Growth Inhibitors in Site Preference of Metastasis

Metastatic cells also receive and process negative paracrine growth signals. For the most part these have turned out to be common inhibitory factors, such as the transforming growth factor-beta (TGF-β) cytokines. Certain organs release potent inhibitors that prevent and, along with positive growth factors, regulate the growth of a variety of metastatic cells. For example, kidney-conditioned medium is particularly inhibitory for many metastatic systems, and these systems uniformly fail to metastasize to the kidney [13–15]. One of the most potent growth inhibitors released into kidney cell-conditioned medium was purified and identified as TGF-β_1 [43]. Cytokines such as TGF-β_1 are known to differentially stimulate or inhibit the growth of cell subpopulations of highly metastatic cell lines [44]. Mooradian et al. [45] found that a poorly metastatic melanoma clone was stimulated to grow by TGF-β_1 in monolayer culture, whereas a highly metastatic clone was not. Growth of the metastatic cells was also stimulated under colony growth conditions in semi-solid medium, but this result does not occur in every metastatic system. Recently established human colorectal and renal carcinoma cell clones from individual tumors exhibited either clonal growth stimulation or inhibition by TGF-β_1 [46], suggesting that there is no simple relationship between metastatic potential and the response of malignant cells to a given growth factor or inhibitor [21].

Melanoma cells in the more advanced vertical growth phase failed to respond to several cytokines, particularly to negative growth cytokines [47], suggesting loss of paracrine growth response with tumor progression. One of the molecules responsible for differentially inhibiting the growth of melanoma cells in the lateral, but not the vertical, growth phase was shown to be IL-6 [47]. One of the important properties of highly malignant cells is apparent loss of paracrine growth inhibitor response [21].

Sources of Paracrine Growth Factors and Inhibitors

The sources of most paracrine growth factors and inhibitors are parenchymal cells, fibroblasts, endothelial cells, mast cells, and macrophages [21]. In some cases the host cells may present the factors on their surfaces. For example, Sargent et al. [48] found that liver growth factors for murine melanoma cells were present on the cell surfaces of hepatocytes. However, tissue-derived cytokines are usually found in the soluble state. Using lung- and liver-colonizing murine large-cell lymphoma cells, Hamada et al. [49] found that conditioned medium from syngeneic organ-derived microvessel endothelial cells could substitute for organ tissue-conditioned medium in tumor cell proliferation assays. Removal of Tf from the lung endothelial cell-conditioned medium reduced mitogenic activity, but some activity remained that was not associated with Tf. Since endothelial cells respond to angiogenetic factors released by tumor cells, a bidirectional or reciprocal relationship may exist between these two types of cells at the secondary site (fig. 1). This *reciprocal cytokine regulation of growth* [21] probably also extends to other cell types as well as to the extracellular matrix. Metastatic growth explosion at certain sites can be most easily explained by the notion that reciprocal cytokines stimulate the growth of both tumor and host cells [21].

In addition to endothelial cells, fibroblasts isolated from different tissues are important producers of paracrine factors. The presence of fibroblasts isolated from dermal tissue generally inhibited the growth of early (lateral growth phase) human melanoma cell lines but had stimulatory or little effect on more advanced (vertical growth phase) melanoma lines [50]. One of the inhibitory cytokines responsible was identified as IL-6 [47]. Okumura et al. [51] found that the conditioned medium from short-term, but not long-term, cultures of fibroblasts from particular organs stimulated the growth of highly metastatic mammary carcinoma cell clones. The highest growth stimulation occurred in medium containing fibroblasts isolated from the lung or mammary gland, the most likely metastatic targets [51]. In contrast to the results with lateral-growth-phase human melanoma cell lines [50], growth of poorly metastatic mammary adenocarcioma cell

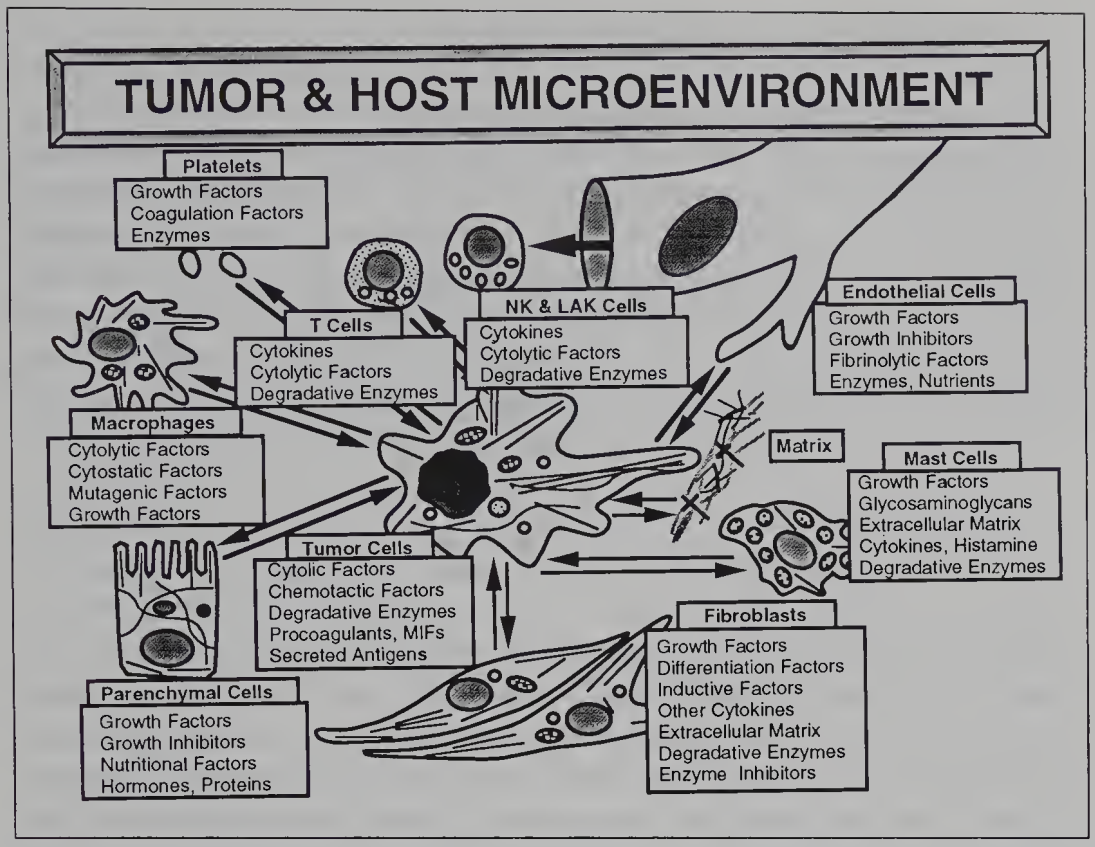

Fig. 1. Bidirectional interactions between malignant cells and their cellular microenvironment. Tumor cells release cytokines that can affect host cells such as parenchymal cells, endothelial cells, fibroblasts, mast cells, granulocytes, and macrophages as well as the host tissue extracellular matrix. In turn, the host cells and matrix release factors that stimulate or inhibit tumor cell proliferation [from 21, with permission].

lines was not inhibited by the mammary or lung fibroblasts [51]. Only the most poorly differentiated high-grade, invasive bladder carcinoma cells were stimulated to grow by bladder-derived fibroblasts [52]. Similarly, Gleave et al. [53] found bidirectional stimulation of prostate carcinoma cells and bone fibroblasts (fig. 1); bone is a common site of prostate metastasis.

Metastatic cell growth can also be stimulated by tumor-invasive normal cells. Mast cells can be attracted by the release of mast cell mediators to the tumor periphery where they produce mitogens and motility factors. Dabbous et al. [54] found that highly metastatic, but not poorly metastatic, rat mammary adenocarcinoma cells attracted large numbers of mast cells, which released factors that differentially stimulated the growth of the metastatic cells. Furthermore, when animals were administered mast cell stabilizers that prevented the release of mast cell contents, the growth and metastasis of the mammary adenocarcinoma cells were reduced [54].

Autocrine Growth Mechanisms in Metastasis

Tumor cells have the capacity to produce growth factors that can act in an autocrine manner [55]. Tumor cells that can condition their microenvironment with the release of cytokines can also produce effects on neighboring cells that do not release similar cytokines [56]. One of the effects of interclonal tumor cell interactions is to change the expression and display of cell surface growth factor receptors. For example, interclonal interactions between murine melanoma cells altered the expression of a cell surface receptor [57] that was later identified as a Tf receptor [58]. The interactions stabilized the expression of Tf receptors and the metastatic properties of the cells [57].

Autocrine loops can be established in cells by the transfer of a growth factor gene or growth factor receptor gene [21, 55]. The transfer of a growth factor gene does not necessarily result in neoplastic transformation, unless the encoded growth factor is synthesized in a form that can be secreted and can establish an autocrine loop. Rogelj et al. [59] transferred the *bFGF* gene fused to a signal peptide that facilitated bFGF secretion. Although the *bFGF* gene alone did not transform the recipient cells, the chimeric signal peptide-*bFGF* gene did, suggesting that autocrine signaling mechanisms are important in neoplastic transformation. In general, as tumors progress to more malignant phenotypes, they become less dependent on serum-derived growth factors [60] and begin producing their own polypeptide growth factors. However, autocrine production of a growth factor does not always correlate with tumor progression or metastasis; examples include a melanoma growth-stimulating factor secreted by melanoma cells [61] and a bombesin-like factor (a gastrin-releasing peptide) secreted by small-cell lung carcinoma cells [62]. The more likely result is a loss of growth factor requirements with tumor progression [63]. Kath et al. [64] sequentially selected human melanoma cell lines from a primary melanoma for their ability to invade a reconstituted basement membrane and showed that only the most invasive variants were spontaneously metastatic in nude mice and less serum-dependent in culture. Selection for growth in serum-free medium resulted in an increase in both invasive and metastatic properties, but the selected variants were unstable and, in the absence of selective pressures, reverted back to their original properties.

Several investigators have used gene transfer techniques to test for autocrine growth mechanisms in metastasis. Eagan et al. [65] found that cells transfected with a transforming signal peptide-*bFGF* chimeric gene construct formed experimental metastases. Untransformed cells have also been transfected with genes encoding factors that they do not normally respond to. NIH 3T3 cells are unresponsive to the colony-stimulating factor CSF-1 because they lack the CSF-1 receptor. Using v-*fms*-transfected cells (that as a result express a

CSF-1-like receptor), Eagan et al. noted that addition of exogenous CSF-1 stimulated cell growth and experimental metastasis. Addition of exogenous CSF-1 to the v-*fms*-transformed cells before injection into animals resulted in increased numbers of experimental metastases, but if the v-*fms*-transformed cells were grown under conditions in which autocrine growth factor conditioning occurred, the cells formed fewer metastases [65]. This suppressive effect was probably due to down-regulation of the CSF-1 receptors on the v-*fms*-transfected cells. Use of widely different concentrations of certain growth factors can have opposite effects on the same cell system. In addition, the transfer of foreign genes into potentially unstable cells can result in cellular diversification and heterogeneity of these cells [66].

Loss of Cytokine Responses in Highly Metastatic Cells

As tumors progress to increased malignancy, they often become less responsive to regulation by exogenous growth factors. An example is the loss of estrogen dependency of MCF-7 breast cancer cells after transfection with the v-H-*ras* oncogene [67]. In contrast to parental MCF-7 cells, the *ras*-transfected MCF-7 cells were tumorigenic in the absence of estrogens and secreted elevated levels of autocrine cytokines. Since advanced breast cancers often become refractory to estrogens and other hormones [68], this finding suggests that highly malignant cells are less dependent on systemic hormones and secrete higher amounts of autocrine growth factors. Breast cancers that are initially responsivé to 17β-estradiol lose hormone responsiveness as they progress to more aggressive phenotypes [68], while their synthesis and secretion of autocrine cytokines increases [69].

Growth Responses and Tumor Progression

As tumors progress, the most malignant cells can lose growth factor and inhibitor responsiveness [21]. This loss in highly metastatic cancers and the ability of such cancers to colonize distinct secondary sites may be explainable by considering the growth properties of cancers at various stages of progression. When cancers progress to early metastatic stages, they often show restricted organ distribution or organ specificity, whereas at the final stages of cancer progression, near host death, they often colonize multiple organ and tissue sites. The most reasonable cause for this is that cancer cells progress from mainly paracrine stimulatory and inhibitory growth mechanisms at the initial stages of metastatic progression to mainly autocrine stimulatory mechanisms at

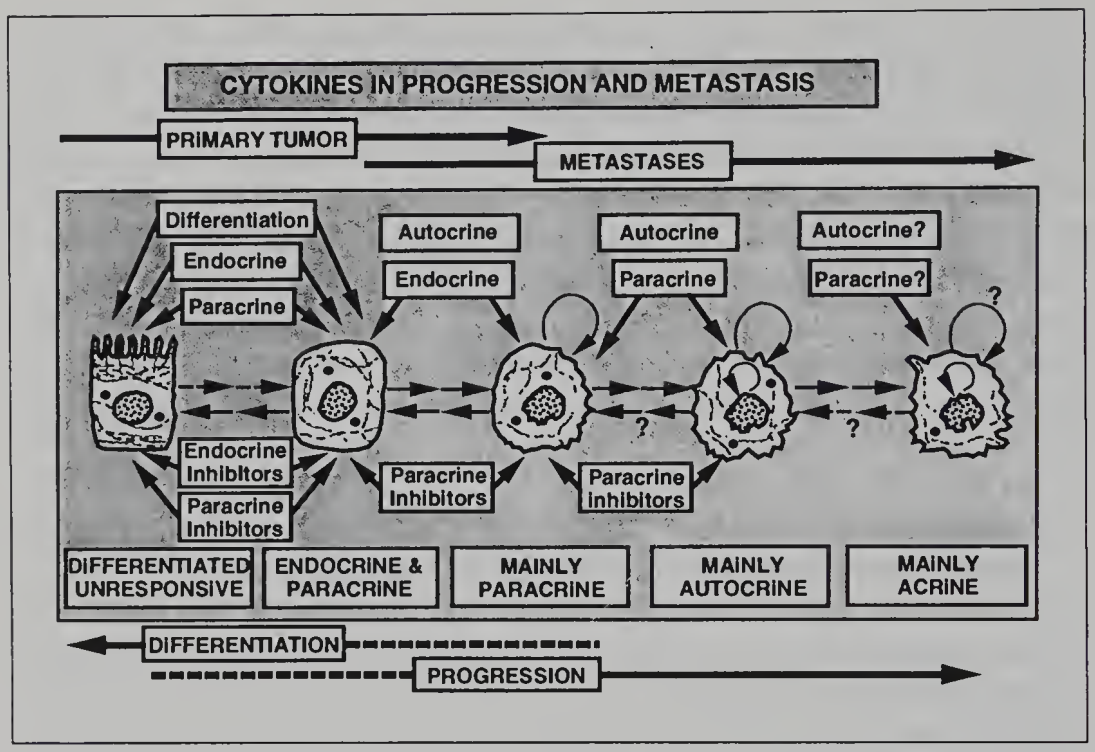

Fig. 2. Progression of malignant cancer cells results in both alterations in their responsiveness to host-derived growth stimulatory and inhibitory molecules and synthesis of autocrine growth factors. Tumor differentiation is shown as a possible process to the left and tumor progression, to the right. Tumor progression can result initially in an increase in paracrine growth factor response, as occurs in organ specificity of metastatic colonization. As tumor progression continues, however, paracrine growth factor and growth inhibitor responsiveness occurs, and increases in autocrine growth factor production become apparent, as do more widespread tissue metastatic colonization properties. Eventually, tumor progression can result in complete loss of growth factor/inhibitor response (an acrine state) and in metastatic colonization of virtually any tissue [modified from 21, with permission].

the terminal stages of progression (fig. 2). Highly advanced cancers secrete a variety of growth factors that could serve as autocrine sources of growth stimulation, and such properties tend to make these cancers more independent of their microenvironments. As metastatic progression continues, the accumulation of alterations in tumor cells produce an acrine (lack of regulation) state in which malignant cells have lost their usual growth regulation properties [21]. Since malignant cells are expected to lack responses to endogenous or exogenous growth factors or inhibitors and to have altered signal transduction or nuclear signaling pathways that are constitutively active, they should be autonomous and relatively unregulated (fig. 2).

Changes in cancer cell growth response with progression have significant implications for the development of new therapies for metastatic cancers. As I

have discussed, metastatic cells should be more refractory to growth regulation by paracrine and autocrine growth mechanisms, making it unlikely that therapeutic intervention using analogs of growth inhibitors, monoclonal antibodies against growth factor receptors, or other means of blocking growth mechanisms will be useful in the treatment of highly advanced cancers [21]. In addition, highly advanced cancer cells are usually unstable and rapidly produce unstable progeny [56]. Thus it is even more unlikely that therapies based solely on growth properties of malignant cells will succeed in eradicating the most highly metastatic, unstable cells. Thus, therapies based on growth properties are probably the most useful at the early stages of malignant progression or the earliest stages of metastasis [21].

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Lymphoscintigraphy: Importance to Cancer Detection and Radiation Treatment Planning

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Radionuclide lymphoscintigraphy is performed by administering interstitial injections of small volumes (0.1–0.3 ml) of a radiocolloid which is nontoxic and chemically inert. The study can be easily repeated, the side effects are in essence nonexistent, and the total body radiation burden is low, of the same order of magnitude as other diagnostic radionuclide studies. This technique allows visualization of lymphatic channels and lymph node groups.

General Concepts, and Indications in Breast Cancer

Selection of a radiocolloid for lymphoscintigraphy emphasizes particle size. In a review by Strand and Persson [1] using an animal model, it was shown that the migration rates from the injection site to regional lymph nodes varied dramatically depending upon the size of the radiocolloid utilized, with ^{99m}Tc antimony trisulfide colloid showing optimal nodal uptake (Best Industries, Springfield, Va., USA).

Internal Mammary Nodes

One of the primary uses for radionuclide lymphoscintigraphy in our institution has been for the evaluation of patients with cancer of the breast. Certainly, the nodes of the internal mammary chain (IMC) lend themselves to this scintigraphic technique inasmuch as they cannot be routinely visualized by other radiologic tests unless they are significantly enlarged.

[1] I thank the technical staff of our Division for generating the clinical data that made this review possible, and Regina Edwards for her efforts in the preparation of the manuscript.

Table 1. Potential pathways of breast lymphatic drainage [from 3]

Nodes seen (percent of cases)	Injection site				
	UIQ	LIQ	UOQ	LOQ	areolar
Axillary only	38	14	64	36	80
Internal mammary only	6	30	2	10	0
Axillary and internal mammary	50	54	30	50	20
Axillary, internal mammary and supraclavicular	6	2	4	4	0

U=Upper; L=lower; I=inner; O=outer; Q=quadrant.

Collier et al. [2] showed that 71% of the IMC nodes detected by lymphoscintigraphy were not appreciated on concomitant CT scan. Indeed, CT image interpreters were unable to distinguish nodal structures from normal vessels and routinely missed defining the majority of lymph nodes, since these 'normal' structures have maximum diameters on the order of 1–2 mm.

Some 20 years ago, Vendrell-Torne et al. [3] showed that intramammary injections of colloidal ^{198}Au in the four breast quadrants, as well as the subareolar region, led to variable scintigraphic results depending upon the site of injection. For example, upper outer quadrant injections resulted in axillary node visualization exclusively in 38% of patients, IMC visualization exclusively in 6%, a combination of axillary and IMC nodes in 50%, and axillary, IMC and supraclavicular node visualization in 6%. These investigators clearly demonstrated that the IMC nodes serve as a drainage route from all quadrants of the breast (table 1). The frequency of IMC node involvement by metastatic breast cancer has been recently reviewed by Solin [4], and appears to correlate with the presence of metastases to the axillary nodes, central or inner quadrant breast lesions, the size of the primary breast tumor, patient age, and prognosis.

Technique

Ege [5] was the first to summarize results of a large experience on the ability to routinely visualize the IMC following a subcostal, posterior rectus sheath injection of 0.1–0.2 ml of ^{99m}Tc antimony trisulfide colloid (18.5 MBq). We follow her suggestions in performing studies at our institution. With the patient supine, injection is administered at a point approximately 3 cm inferior to the xiphoid process and 1–2 cm medial to the midclavicular line of the side under study. The depth of injection is controlled by applying tension to the skin and underlying rectus muscle with the free hand. The radiocolloid is deposited at a depth of approximately 2 cm, just anterior to the posterior rectus sheath;

therefore the needle traverses skin, subcutaneous tissue and the rectus muscle, and stops just short of the peritoneal cavity.

Initial images at 1 h and delayed images at 3 h will show an elliptical injection site and at least one discrete node which denotes the origin of the IMC. A scintiphoto of the anterior thorax at 3 h (which excludes the injection site) will show well-defined internal mammary nodes from the paraxiphoid area, through the thorax, to the level of the supraclavicular nodal group. Quantitative studies have shown that these elegant images are produced with $<1\%$ of the injected dose migrating from the injection site to the entire lymphatic chain [6]. This injection technique results in a reproducible and reliable methodology for visualizing the IMC [5].

Three-Dimensional Localization

One of the primary indications for performing radionuclide lymphoscintigraphy of the IMC is to ensure adequate radiation portal coverage. Arguments for and against such therapy are discussed by Levitt [this volume] and by Solin [4]. We have utilized this technique in the radiation therapy planning of many hundreds of patients, and have found the 3-dimensional localization of these nodal groups to be informative and – most importantly – unique to each individual patient.

Ohtake et al. [7] demonstrated that measurements of nodal depth could be obtained by using a stereo lymphoscintigraphic technique, thus obviating the need for individual anterior and cross-table lateral scintiphotos. They used a bilateral slant hole collimator to produce a single anterior view, allowing depth determination of each individual lymph node from the two scintigraphic images.

At our institution, Siddon et al. [8] have adapted this technique to the single slant hole collimator, which is routinely available in many nuclear medicine departments as an aid to cardiac imaging. We obtain a double scintigraphic exposure with the collimator rotated 180° between each image set. Therefore, the calculations are not as influenced by the shape of the sternum or the patient's transverse contours.

Information from 167 consecutive patients evaluated in this manner revealed that between rib 1 and interspace 5, 768 nodes could be defined (table 2) [9]. About 75% of these nodes were located between ribs 1 and 3; of more importance however was the appreciation of the degree to which these nodes splay out laterally from the midline as one moves from the subcostal site of injection to the sternal notch. Similarly, these more cephalad nodes show a marked increase in depth when compared to nodes located posterior to the lower ribs and interspaces. Indeed, the old adage of nodes usually being 'positioned within 3 cm of midline and within a 3 cm depth to the sternum' is

Table 2. Distribution of 768 internal mammary lymph nodes by rib/rib interspace (IS) in 167 patients [from 9]

Site	n	%
Rib 1	56	7.3
IS 1	132	17.2
Rib 2	144	18.8
IS 2	128	16.7
Rib 3	93	12.1
IS 3	74	9.6
Rib 4	49	6.4
IS 4	35	4.5
Rib 5	36	4.7
IS 5	21	2.7

Table 3. Percent of patients with at least one node outside the tangential fields, as a function of beam edge entry distance contralateral to midline [from 10]

	Distance from midline, cm						
	3.0	2.5	2.0	1.5	1.0	0.5	0.0
Patients, n	31	45	58	70	93	103	128
% out	19	27	35	42	56	62	77
% in	81	73	65	58	44	38	23

quickly dispelled when reviewing the scintigraphic depiction of the 3-dimensional anatomic localization of these nodes.

In terms of incorporating the IMC when utilizing opposing field tangential beam radiation therapy to treat both breast tissue and internal mammary nodes, the issue of the entry point of the medial beam is critical. When we looked at the percent of patients with at least one node which would have been outside the tangential field as a function of beam edge distance from midline, it was obvious that as one moved farther contralateral from midline, this percentage decreased (table 3). At a 0.0 medial beam entry point, 77% of patients had at least one node outside the tangential field, whereas a medial beam entry point of 3.0 cm contralateral to midline resulted in only 19% of patients having at least one node outside the tangential field [10].

However, one must also look at the information available from radionuclide lymphoscintigraphy when individually tailoring the radiation port for a specific patient. For instance, even though beam entry at midline resulted in 77% of patients having at least one node outside the tangential field, the remaining 23% of patients had *all* lymph nodes included (table 3). This is certainly of primary importance with our current increased efforts towards sparing normal pulmonary parenchyma and cardiac tissue.

Identifying Metastases

Radionuclide lymphoscintigraphy of the IMC can also be used to identify sites of metastatic involvement within nodes. Indeed, abnormalities in radionuclide lymphoscintiscans can be detected long before nodal enlargement is appreciated by thoracic CT scans or lateral chest X-rays.

The rationale behind this diagnostic radionuclide approach is that tumor cells migrating through the lymphatics aggregate within lymph nodes and compromise normal phagocytic capacity as detected by radiocolloid imaging. One could think of the lymph node scintiphotographic image as a 'mini liver scan' with compromised reticuloendothelial cells producing areas of heterogeneity and focal decrease in radiocolloid uptake. Consequently, the nuclear medicine physician should be able to detect mottled or patchy uptake, asymmetry of uptake (if one looked at the ipsilateral vs. normal contralateral IMC) and a failure of radiocolloid to migrate in the lymphatic channel beyond the point of partial or complete obstruction.

Matsuo [11] looked at the correlation of internal mammary lymphoscintigraphy images and internal mammary node biopsy in 73 patients. This is one of the few, if not the only, large series which actually correlated histologic with scintigraphic data. They found an imaging sensitivity of 100% and a specificity of 96%. In another study, a highly positive correlation was found between the abnormal IMC lymphoscintigraphy result and the incidence of distant metastases and local recurrence. Ege and Clark [12], in a review of 249 patients who underwent partial mastectomy followed by internal mammary lymphoscintigraphy, showed a 3-fold increase in the incidence of distant metastases and a doubling in the incidence of local recurrence in patients who evidenced a positive or abnormal internal mammary lymphoscintigraphic study when compared to those in whom the scintigraphic results showed normal uptake of radiocolloid in the internal mammary nodes.

Axillary Nodes

Radionuclide lymphoscintigraphy of the axillary lymph nodes may have a very specific role to play, particularly in patients being considered for radiation therapy. Larson et al. [13] showed that there was an increase in actuarial risk of

Table 4. Relationship of node visualization with radionuclide lymphoscintigraphy, subsequent radiotherapy and development of edema in 202 patients [from 14]

Nodes seen	Radiotherapy	Edema (%)
Yes	No	5/48 (10)
Yes	Yes	20/82 (24)
No	No	6/29 (21)
No	Yes	14/43 (33)

developing lymphedema following radiation therapy if patients had undergone prior axillary surgery. Of 235 patients treated with irradiation in whom no pretherapy axillary surgery was performed, there was a 4% 6-year actuarial risk of developing arm edema. This was opposed to a 13% risk in a comparable group of 240 patients who did undergo some axillary node sampling prior to external beam therapy.

Frühling and Bourgeois [14] have utilized radionuclide lymphoscintigraphy of the axillary lymph nodes to predict whether or not patients would develop lymphedema of the upper extremity following radiation therapy. They showed that 24% of patients in whom axillary lymph nodes were visualized by lymphoscintigraphy and then had radiation therapy involving the axilla developed lymphedema. This number increased to 33% when lymphoscintigraphy before irradiation failed to visualize axillary nodes (table 4).

When Larson et al. [13] looked at the type of axillary surgery performed preceding radiation therapy and estimated the subsequent risk of arm edema, the numbers were predictable. In those 85 patients who underwent only lower axillary node sampling, there was a 5% risk as opposed to an 8% risk in those who underwent lower axillary node dissection. With full nodal dissection, however, there was a 37% actuarial risk of developing lymphedema of the upper extremity following radiation therapy.

Lymphatic Surgery

An important additional therapeutic application of radionuclide lymphoscintigraphy to the patient with treated breast cancer is in the *evaluation* of secondary upper extremity lymphedema [15, 16]. Contrast lymphangiography in this patient group is contraindicated as a diagnostic tool: in addition to the fact that lymph vessels in an edematous extremity are difficult to localize, there is potential for localized obstructive lymphangitis, skin necrosis from dermal

backflow of the contrast material, and formation of sterile abscesses, as well as a small potential for an allergic response to the contrast material.

Intradermal injections of radiocolloid on the dorsum of the ipsilateral hand (as opposed to interdigital injections) result in excellent definition of the status of the lymphatic channels – of key concern to the vascular surgeon asked to consider these patients for either subcutaneous resection or lymphaticovenous anastomosis. In the normal patient, intradermal injections (0.1–0.3 ml; 18.5–37 MBq) of radiocolloid will show rapid migration of tracer from the injection site with visualization of 1–3 main channels over the posterior wrist and forearm within 1–3 min after injection. The radiocolloid then transits medially through the antecubital fossa to the medial upper arm, terminating in the axillary lymph nodes.

Indeed, tracer migration from the injection site is so rapid that we encourage that imaging commence *immediately* upon injection, since in the abnormal arm appearance of radiocolloid dermal backflow within 5–10 min after injection can totally obscure the visualization of any discrete lymph channels. The abnormal arm will commonly show a slower pattern of tracer migration via lymphatic channels, which may be collateralized and tortuous resulting in poor visualization of the more proximal lymph channels and absent visualization of the axillary lymph nodes at 1 h.

A failure to visualize channels in an edematous extremity should be followed by a repeat lymphoscintigraphy study after the edema has been reduced by either gravity or use of a commercial compression pump device. It is only after this maneuver that 'nonvisualized' channels can be reliably reported.

In our experience, it is not uncommon to detect areas of abnormal radiocolloid migration in patients who are totally without symptoms or signs at the time of the study. The scintiphotos will depict collateralized vessels or regional areas of dermal backflow which upon physical examination appear normal. It is invariable, however, that when questioned the patient will comment that this is the precise area of regional lymphedema associated with symptoms.

Malignant Melanoma

A prospective 'controlled' lymphoscintigraphic study of patients presenting for treatment of cutaneous truncal malignant melanoma cannot, for obvious ethical reasons, be performed. We can however evaluate the results of preoperative lymphoscintigraphic and clinical estimates of drainage patterns compared with postoperative results to estimate the degree of discordance between clinical and lymphoscintigraphic approaches.

Table 5. Number of nodal groups visualized following truncal radionuclide lymphoscintigraphy

Reference	Nodal groups visualized								total patients
	1		2		3		4		
	n	%	n	%	n	%	n	%	
19	27	54	16	32	4	8	3	6	50
20	5	46	4	36	2	18	0	0	11
21	23	47	24	49	0	0	2	4	49
22	4	31	5	38	3	23	1	8	13

Table 6. Number of patients demonstrating nodal drainage beyond anatomic watershed with truncal radionuclide lymphoscintigraphy

Reference	Watershed pattern				Total patients
	inside		outside		
	n	%	n	%	
19	22	44	28	56	50
20	4	36	7	64	11
21	23	48	25	52	49[a]
22	5	38	8	62	14

[a] 1/49 patients not included.

Table 7. Frequency of axillary node visualization with truncal radionuclide lymphoscintigraphy

Reference	Patients	
	n	%
19	48/50	96
20	11/11	100[a]
21	21/25	85
22	12/13	92

[a] All lesions located at or above Sappey's line.

Staging

A key point in the appreciation of the interrelationship of predicted versus actual drainage patterns is the concept of a 'lymphatic watershed'. This watershed concept, based on the early work of Sappey [17], defines a line approximately 2.5 cm on either side of the anterior and posterior midline of the trunk as well as a second line which angles anteriorly from the second lumbar vertebral body to the umbilicus. These lines, or zones of lymphatic anatomic variation, in theory define the boundaries of lymphatic drainage pathways.

For example, a lesion located on the left anterior chest wall, just lateral to the areolar region, should – by definition of lymphatic watershed anatomy – drain to the left axilla. However, data generated both from clinical experiences [18] and from lymphoscintigraphic experiences show that this is not always the case. In fact, the drainage of truncal lesions is for all practical purposes unpredictable by conventional anatomic guidelines in an individual patient.

A number of studies have addressed the issue of lymphatic drainage from truncal lesions by use of intradermal injections of ^{99m}Tc antimony sulfide colloid [19–22]. In reviewing these series, it becomes apparent that there are at least three unifying findings which underscore the utility of this radionuclide technique in evaluating patients presenting with truncal melanoma. These include: (a) the number of nodal groups visualized during radionuclide evaluation of solitary truncal lesions; (b) the relationship of drainage patterns to the classical descriptions of 'watershed' anatomy, and (c) the frequency of axillary lymph node drainage from truncal lesions. Let us now look at each of these parameters.

When one looks at the mean number of nodal groups identified following truncal radionuclide lymphoscintigraphy, only 45% (range 31–54%) showed drainage to a solitary nodal group. Indeed, the results among the series are strikingly similar with respect to the number of patients in whom 2, 3, or 4 nodal groups are visualized during the radionuclide investigation of a solitary truncal lesion (table 5).

If we consider the likelihood that the lymphatic drainage of a lesion is confined to its 'watershed' area, we are again impressed by the infrequency with which this event occurs. Of a total of 122 patients, less than half (range 36–48%) demonstrated lymphatic drainage confined to the watershed area. Indeed, between 52 and 64% of patients showed cutaneous communication to lymph node groups beyond the predicated anatomic watershed area (table 6).

Munz et al. [19] specifically addressed the frequency with which axillary lymph node groups are visualized in patients presenting with truncal lesions. Their study documented a 96% incidence of such a phenomenon. When one critically analyzes such patients from other series, the numbers are again strikingly similar [20–22] (table 7). An awareness of the frequency of this event

Table 8. Correlation of clinical prediction of nodal drainage versus scintigraphy with truncal radionuclide lymphoscintigraphy

Reference	Concordant		Discordant	
	n	%	n	%
20	6/11	55	5/11	45
21	9/21	43	12/21	57
22	4/10	40	6/10	60

is of importance to the surgeon planning a presumed 'curative' dissection of a regional, nonaxillary lymph node group.

The inability to predict the pattern of lymphatic drainage from a truncal lesion by a combination of clinical experience and knowledge of the regional lymphatic anatomic pathways has been carefully documented [20–22]. The surgeons involved in these studies recorded their prelymphoscintigraphic impressions of those nodal groups likely to be identified following radionuclide evaluation. The results of these studies, which evaluated 42 such patients, showed that the clinical prediction and the radiolymphoscintigraphic data were discordant in approximately one-half (range 45–60%) of the patients studied (table 8).

Surgeons associated with the Sullivan study [20] at Duke University Medical Center operated on 19 patients and correlated the results of radionuclide lymphoscintigraphy with pathology. In each case, the lymph node group selected for resection was one identified by radionuclide lymphoscintigraphy. The number of nodes examined per patient ranged from 7 to 55. Metastatic tumor was identified in the tissue from 12 of the 19 patients, and these metastatic sites were noted to involve four or fewer nodes in all but 1 patient.

What is apparent from Sullivan's study [20] is that the lymphoscintigraphic identification of nodal groups which drain a cutaneous lesion is a valid predictor of the in vivo experience of tumor cells, and that this technique can allow the surgeon to document those nodal groups at high risk for malignant involvement. Munz et al. [19] stressed that the lymphoscintigraphic data do not necessarily indicate nodal metastatic disease per se.

Although the preceding data were restricted to the evaluation of patients with truncal lesions, the technique is certainly applicable to patients presenting with malignant melanoma of the scalp or extremities. In particular, Sullivan et al. [20] have documented that lymph drainage from the most proximal aspect of the extremities (i.e. the shoulders and buttocks) is also ambiguous, and

lymphoscintigraphic studies are likely to be informative in such cases. Even more striking in their experience was the incidence of discordant results when attempting to correlate the clinical prediction of lymph node groups draining scalp lesions versus the nodes identified by radionuclide lymphoscintigraphy. In the 3 patients in their series presenting with scalp lesions, all showed discordant results leading to significant curtailment in the proposed surgical approach and a more conservative course of patient management.

Recurrence

Logic and Balch [21] have predicted a site of recurrence of malignant melanoma which developed in a nodal area initially identified by radionuclide lymphoscintigraphy but not considered clinically at risk by the surgeon. A similar experience has been reported by Fee et al [23]. Additional follow-up studies will be necessary to define the significance of these phenomena and whether or not more aggressive surgery at the time of initial patient therapy will alter survival. For the present however, intradermal radionuclide lymphoscintigraphy has been shown capable of identifying the pathways of lymphatic drainage from sites of cutaneous malignant melanoma. The procedure is simple to perform and allows the clinician to intelligently approach each patient with full knowledge of the specific ambiguities of lymphatic drainage.

Conclusion

Radionuclide lymphoscintigraphy is physiologic, noninvasive, easily performed and readily repeated. The study results offer information on the functional capacity of lymphatic channels and lymph nodes, their 3-dimensional location in space, and in selected instances, the presence of metastatic deposits. This diagnostic tool should be considered whenever the pathophysiology of lymphatics is in question.

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Effects of Ionizing Radiation on Lymph Nodes

A Review

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Lymph nodes are a large and important compartment of the lymphopoietic system and contain both B and T lymphocytes. Their radiation sensitivity is, therefore, intimately related to that of lymphocytes.

Radiosensitivity of Lymphocytes

Lymphocytes are among the most radioresponsive cells in mammals. Cytotoxic effects have been detected in vitro with doses as low as 2–5 rad [1]. In the 1960s and 1970s, numerous in vivo and in vitro experiments were designed to measure precisely this sensitivity [2–4]. Table 1 summarizes some of the data obtained in those decades, as reviewed by Anderson and Warner [3]. Overall, B cells are more radiosensitive than T cells, however there are subpopulations within both cell types that show greater or lesser response [4]. In general it can be said that proliferating lymphocytes (B and T) are quite radiosensitive and die rapidly, while mature nonproliferating cells are resistant. Thus mature secretory B cells, especially plasma cells [5], are radioresistant. Effector T cells (suppressor, cytotoxic and helper) are also radioresistant to variable degrees (see table 2) [3].

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Table 1. Radiosensitivity of lymphocyte subpopulations

Subpopulation	D_0, R
B-cell viability	40
B-cell Ab production	70–145
Most studies	<100
T-cell viability	100
T-cell proliferation	64
T-cell response (GvH)	74–100
T-dependent humoral response	50–214
Most studies	<100
T-cell response (helper)	230

R = Roentgen.
From various authors (1962–1975); quoted by Anderson and Warner [3].

Table 2. Radiation response of T-cell subsets [3]

T-cell subset	D_0, R
Helper	
Unprimed = sensitive	230
Primed = resistant (activated)	2,000
Suppressor	
Precursor = sensitive	
Effector = resistant (activated)	$>2,000$

There are many studies of the in vivo sensitivity of lymphocytes. It is known that whole body (WB) irradiation with a dose as low as 25 Roentgens (R) produces a significant depletion of blood lymphocytes [3]. A higher WB dose of 100 R causes a rapid loss of 25% of the blood lymphocytes in the rat [3, 5]. The recovery from this lymphopenia is slow (years). T cells recover first but do not reach pretreatment levels for a long time [5].

It is also known that, unlike many other cells, radiation-induced death of the sensitive lymphocytes occurs in interphase rather than during the mitotic cycle [3]. It is also known that most radioresistant T lymphocytes that survive radiation can die if stimulated to proliferate [3]. The effects of radiation on lymph nodes can be subclassified as structural – or morphological – and functional.

Morphology of Experimentally Irradiated Lymph Nodes

There are numerous experimental studies documenting the morphological changes that occur in lymph nodes following various doses of local or WB irradiation. In two such studies [6, 7], the early nodal alterations were evaluated sequentially by transmission electron microscopy: after a single dose (SD) of 3,000 R the earliest lesions were detected by 8 min [6]. A SD of 500 R resulted in lesions detectable at 30 min and characterized by swelling of cytoplasmic projections [7]. At 60 min there was margination of chromatin.

A SD of 350 R produced by 2 h nuclear vacuoles that could be observed by light microscopy, followed by progressive karyopyknosis, contraction of the nucleus, karyorrhexis (which became maximal at 12 h), disintegration of the cytoplasm and finally removal by macrophages. By 24 h most lymphocytes in irradiated nodes receiving 350 R were absent [8].

WB exposures of 600–800 R SD in rabbits caused extensive acute necrosis of lymph node lymphocytes, with maximum accumulation of debris at 8 h [8]. This debris disappeared by 16 h. Segmented granulocytes invaded diffusely the nodes at this early stage. Regeneration of lymphocytes began at 5–9 days and was diffuse initially. By 21 days, small actively proliferating germinal centers appeared. The entire lymphatic tissue was reconstituted by 59 days. The complete reconstitution occurred earlier in rats given 600 R SD exposures, but the sequence of events was similar [8].

For this recovery and repopulation, the presence of bone marrow and/or splenic cells is necessary. The lymphocyte traffic required for repopulation is controlled by multiple cellular and humoral factors; among these are prostaglandins which down-regulate it [9].

Two favorite sites for the study of *local* radiation effects are the lymph nodes in the knee and renal area of rats [10]. Using these nodes, the following observations have been made (table 3): after a local SD of 3,000 R, there is maximum lysis of lymphocytes by 12 h and a remarkable recovery with almost total restoration of lymphocytes at 24 h [10]. A few days later, germinal centers appear, but by 14 days there is a second wave of atrophy. Then there is progressive loss of follicles and lymphocytes although plasma cells remain well throughout. Between 9 and 12 months, there is total eradication of the lymph node architecture by 'fibrosis' and loss of lymphatic tissue. There is also reduction in the number of blood vessels, which are occasionally thickened. On the other hand, the lymph sinuses remain intact. The same delayed effects are observed 28 weeks after 6,000 R delivered in 10 daily fractions of 600 R [10]. Although not identical to the findings of other investigators, these observations underline the rapid depletion and recovery of the lymph nodes

Table 3. Sequential morphology of irradiated lymph nodes [10]

12 h to 88 weeks after a local SD 3,000 R to right knee lymph node or right renal lymph nodes of 3-month-old rats	
12 h:	Maximum lysis of lymphocytes
24 h:	Almost total restoration (few mitoses)
Few days:	Germinal centers reappeared
14 days:	Second wave of atrophy; progressive loss of follicles and lymphs; plasma cells remained Nodal weight decrease: noted at 14 days and progressive
9–12 months:	Eradication of lymph node architecture by 'fibrosis' and loss of lymphatic tissue; reduction in number of blood vessels; lymph sinuses remained intact
600 R daily × 10 fractions:	Similar late changes after 28 weeks

and the subsequent atrophy that results from clinical kilorad therapy to regional lymph nodes.

Most experiments have shown that the stroma of the lymph nodes persists after even high doses [11]. Probably, however, there is damage to the blood capillaries that does not improve (as the lymphatic tissue may) by antigen stimulation. In fact, the high endothelial venules (HEV) show damage by light and electron microscopy from doses between 500 and 750 rad: swelling of endothelial cells and occlusion of the HEV, both in rodent and human marrow recipients [12].

As in other lymphopoietic organs, radiation causes changes in the proportions of nodal cell populations [5]. There is an increase in natural killer cells, macrophages and plasma cells. There is also an increase in the ratio of cytotoxic-suppressor T cells to helper T cells [5]. On the other hand, basophilic granulocytes and mast cells remain stable during the processes of depletion and repopulation [13]. It appears that the dendritic cells of the cortex are less radioresponsive than the lymphocytes [14].

Morphology of Irradiated Human Lymph Nodes

A number of pathologists and various other investigators have become familiar with the morphology of the delayed injury in human lymph nodes. The acute injury is rarely observed in humans because resection of lymph nodes is seldom performed during or immediately after irradiation.

My own experience [15] coincides with that of other observers [16–20]. Following doses between 4,000 and 7,000 rad with the usual fractionation, the following four patterns are recognized:

(1) *Pattern A* (acute, subacute or delayed) consists of lymphocyte depletion, usually incomplete, in the follicles and the paracortex while the stromal skeleton and vessels remain intact.

(2) *Pattern B* (delayed) consists of progressive lymphocyte depletion that can reach total lymphocyte loss. There is also progressive replacement by adipocytes and atrophy of the stroma that may eventually render the lymph node unrecognizable. It is likely that the lymphatic vessels remain patent at this point as in the experimental models, but this is not easy to detect by most pathology techniques. Such fat-replaced nodes should be distinguished from nodes (e.g. axillary) that normally consist of a lymphatic shell with a large ovoid center of adipose tissue.

(3) *Pattern C* (subacute or delayed) consists of fibrosis that may involve the entire node, or more often may be focal and sharply defined. This fibrosis appears to occur in areas of pre-existing tumor that has been eradicated by the irradiation. The fibrosis is usually dense, but may have focal necrosis and occasionally may contain foreign body granulomas. Rarely one can recognize necrotic tumor cells. In a few cases one can even find foci of tumor that may be well preserved, or may show the characteristic nuclear stigmata of recent radiation injury.

(4) *Pattern D* (delayed) is that of a normal lymph node. According to one meticulous study [18], normal lymph node morphology can be seen in as many as 17% of the nodes within a field of kilorad therapeutic irradiation.

Functional Effects of Lymph Node Irradiation

In irradiated lymph nodes, one of the first effects explored was the filter function. The detailed observations of Engeset [10] in 1964 revealed that lymph nodes of the rat knee became more permeable to the passage of human (7 μm) and toad (15 μm) red cells by 2 weeks after a local SD of 3,000 R. This effect increased with time from 7% at 2 weeks to 25% later on. In addition, irradiated lymph nodes became more permeable for Walker carcinoma cells injected distal to the nodes, resulting in a greater number of pulmonary metastases. Also the nodes became more permeable to vaccine (DTP)-induced inflammatory response. However, there was no change in the lymphangiograms up to 1 year. Beyond that time there were shunts that bypassed the lymph node, and it was speculated that obstruction 'by scar' had produced obliteration of the lymphatic drainage through the lymph node [10]. These observations of the 1960s

were supported by two experimental studies published in 1970 [21, 22]. As far as I am aware, the evidence indicating that irradiation decreases the filter function of the lymph nodes is still valid.

That irradiated lymphatic vessels may eventually become obstructed is supported by some clinical evidence. The incidence of lymphedema of the arm following mastectomy with axillary lymphadenectomy increased from 7.4% without radiotherapy to 38.3% with radiotherapy in one study [23].

The effects of radiation on the immune functions of lymph nodes are substantial, of course. The ability of lymphocytes to adhere to the endothelium of the HEV is actually enhanced up to a dose of 150 rad [24]. Above 500 rad it is depressed. At 750 rad, more than 50% of the lymphocytes are unable to enter the peripheral lymph nodes and this effect is dose dependent [24]. This is probably due to damage of ligands on the endothelial cell surface [24]. Incidentally, irradiated thoracic duct lymphocytes also fail to enter lymph nodes, probably due to damage to homing receptors [14]. Therefore it appears that the receptors on the surfaces of both endothelial cells and lymphocytes are altered, interfering with the entry of lymphocytes into the lymph node.

The humoral immune response is also impaired: repeated irradiation of local draining lymph nodes prevents development of both local and distant antibody-forming cells [25]. In other words, local irradiation of a lymph node has not only local but also systemic effects.

Experimental irradiation of the lymphatic organs can result in increased susceptibility to pathogenic organisms and to conditionally pathogenic bacteria [3, 26]. Also there can be increased susceptibility to viral infections [3]. This effect is only seen in acute infections if the challenge follows the irradiation by several days. However, for chronic infections the effect is observed whether the challenge predates, postdates, or is synchronous with the irradiation [3].

Sublethal total body irradiation in humans (e.g. atom bomb survivors) may be associated with a delayed increased susceptibility to chronic infection although this is not clearly proven [3]. There is no clinical evidence that local irradiation of lymph nodes may result in infection(s) despite the experimental results reported above.

On the other hand, acute, severe infections may occur after splenic irradiation in humans [27]. It is pertinent to mention that splenectomy has significant immunologic effects [28]. There is a deficiency in tuftsin (a phagocytosis-promoting peptide), IgM and properdin in response to particular antigens [29]. There is an increased risk for septicemia by encapsulated bacteria such as *Streptococcus pneumoniae, Neisseria meningitidis,* or *Haemophilus influenzae* [28]. There is also a risk for *Babesia microti* infection, although there is no increased risk for most other nonbacterial infections [28]. The incidence of septicemia in splenectomized

patients may be high (1.4–20%) and the infections may be especially severe in children and young adults who receive chemotherapy [29, 30].

Effects of Total Lymphoid Irradiation

Of importance to this discussion are the effects of total lymphoid irradiation, which has been used clinically and experimentally for three main purposes: treatment of lymphomas, induction of tolerance to transplants and treatment of autoimmune disease [31].

Total lymphoid irradiation produces multiple effects in humans (and in some experimental animals as well): there is rapid depletion of blood lymphocytes as well as depletion of cells in the spleen, lymph nodes and thymus. These organs can be reduced rapidly to one-tenth of their original volume [31]. Sequential observations of the blood show that B cells begin to reappear at the second week while T cells begin to reappear at the second month. It takes 2 years to return to near-normal numbers [31]. T cells stabilize at one-half of the pretreatment number while the final percentage of B cells doubles; so, by 10 years the blood B/T ratio is inverted permanently. New subpopulations of immature T cells appear, and there is a dominance of suppressor cells [31].

The response to phytohemagglutinin is depressed for 10 years. The mixed leukocyte reaction is eliminated for more than 2 years. There is a low reactivity to dinitrobenzene. There is tolerance for bovine serum albumin. Thirty percent of these patients remain anergic [31].

Augmentation of Immune Response

Irradiation of the lymphatic tissue does not always inhibit the immune response. There is actually evidence of *augmentation* of the immune response when animals are total body irradiated shortly after immunization [2].

For instance, the hemolysin response to injected sheep erythrocytes increases if followed by 25–100 R [1]. There is also an increase in antibody response to BCG if followed by 400–500 R. Delayed growth of a sarcoma has been shown in mice receiving total body exposure of 400 R on the eighth day after tumor inoculation; this is not caused by a direct effect of radiation on the tumor, since the tumor growth curve in irradiated animals who are given spleen cells is the same as in controls [2]. Thus, the mechanism of this augmentation may not involve lymph nodes only but all lymph organs, and it has been speculated that it is due to injury of regulatory T cells [2].

Conclusion

Ionizing radiation profoundly disturbs lymph nodes in their structure and function. The structural alterations are transient after low doses and permanent after high doses. The functional changes at high doses are also permanent, and their clinical importance depends upon the extent of the irradiated lymphopoietic tissue. Few if any *clinical* effects are evident after *localized* irradiation of lymph nodes. Even total lymphatic irradiation is quite compatible with life. Although the alterations of immune function after total lymphatic irradiation may have implications beyond the many already observed, the clinical benefits appear to outweigh its adverse effects.

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Radiobiology of Subclinical Disease

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Adjuvant radiotherapy and/or chemotherapy for the treatment of patients at high risk of developing regional or distant metastatic disease is of proven value in many cancer situations. However, the decision to use adjuvant therapy is based largely on the presumption that subclinical disease exists, and takes little account of the extent of the tumor burden. Similarly the type of therapy is often chosen with little consideration of factors that might be unique to subclinical tumors, such as their kinetics of growth. Surprisingly little is known about the quantitative kinetics of the often long subclinical phase of human cancer. Most concepts are based on extrapolations from the behavior of tumors during the relatively shorter period when they are clinically obvious, and may be erroneous and misleading. In this presentation we discuss a model for the metastatic process that may aid when designing and evaluating the efficacy of existing and future protocols for the treatment of subclinical disease.

Modelling Subclinical Metastatic Disease

For the purposes of the initial model we will assume that a nodule containing 10^9 tumor cells is the upper limit of clinical nondetectability, i.e. the tumor burden that can be classified as subclinical. If a tumor contains cells that average 10 μm in size, 10^9 cells (2^{30}) will form a nodule 1 cm in diameter, whereas a large nodule of 4 cm diameter will contain 6.4×10^{10} cells (2^{36}). If tumors are assumed to grow exponentially, each exponential increase in tumor volume will take an equal amount of time. It follows that it will take 5 times as

long for a metastasis to reach the upper limits of clinical nondetectability (1 to 10^9 cells) as it will to go from detectable to gross disease of 4 cm (10^9 to 6.4×10^{10} cells). Also if subclinical tumors are treated with radiotherapy (since cell killing by radiation follows an exponential function) the dose to eliminate subclinical disease would be 5/6 of that required to eliminate gross tumors of 4 cm diameter. Not a very big difference!

This analysis is fairly consistent with current clinical radiotherapeutic practice. In the early 1970's, Fletcher [1] and Bagshaw and Thompson [2] advocated elective neck irradiation with around 50 Gy in 2-Gy fractions to both sides of the neck, and demonstrated that tumor recurrence rates decreased from around 35% to around 8%. Since that time the prevailing consensus is that 'the' dose for elective radiotherapy of subclinical disease is of this order.

In fact, primary tumor growth is not exponential but fits better a Gompertzian pattern of growth, slowing with tumor age [3]. However, the little evidence that is available suggests that metastasis growth is better described by an exponential; perhaps because the tumors are smaller when observed. This conclusion has been reached from measurement of the rate of growth of human and murine tumor metastases assessed radiologically [4] and histologically, respectively [5]. The latter study suggested that after lodgment of cells, there was a period of rapid tumor growth up to 0.2 mm diameter (around 8,000 cells) that was limited by the lack of vasculature and accompanied by lymphohistiocytic infiltration. Then another rapid growth phase occurred postvascularization. Overall, growth was consistent more with exponential than Gompertzian models.

If a series of patients are examined, a proportion will never develop metastases following surgery. Another proportion will have clinically detectable metastases at first presentation and can be considered to have in excess of 10^9 cells. The rest will have subclinical disease of between 1 and 10^9 cells. If we assume that the metastatic process proceeds at a constant exponentially increasing rate, then the number of patients with a given log number of subclinical metastatic clonogens will be more or less uniformly distributed over the whole range of metastatic sizes. In other words, as many would be expected to have 1–10 clonogens as would have 10–100, etc. Since 50 Gy given in 2-Gy/day fractions will be expected to kill around 10^7 cells, doses as low as 15 Gy might be expected to cure 20% of those patients with subclinical disease. Also, the tumor control probability curve for patients with subclinical disease would be expected to originate at zero dose and be flat and linear up to 50 Gy. This can be compared with curves for the control of established disease, which show a threshold-sigmoid relationship because they deal with a smaller range of large-sized tumors. If this model is correct, then in situations where the tolerance of normal tissues is compromised it may be worthwhile giving lower doses than

normally prescribed for clinical disease. This does not mean that one should not treat subclinical disease to tissue tolerance, since the tumor burden in any one patient is unknown.

Assumptions of the Model

Clearly there are a number of assumptions in this model, and a number of factors that may influence the outcome have been ignored because their influence is uncertain. For example, small metastases may or may not show exponential growth, and the clonogenicity of tumor cells may be higher in the early phase of metastasis (although the evidence suggests that such factors may not have a major influence [6]). In addition, metastasis is a selective process requiring properties of tumor cells that overcome host defences by creating an immunosuppressive environment [7, 8] or by altering the tumor-host balance [see Nicolson, this volume]. Small numbers of tumor cells may, however, be dealt with immunologically. All these factors are biologically very relevant, although they may not be of sufficient force to influence the linear-exponential nature of the model. Clearly the model needs to be tested with clinically relevant data before conclusions can be drawn as to its usefulness.

Testing the Model

Some initial attempts have been made at testing the model by Withers et al. [submitted for publication] using clinical data culled from the literature. Control rates achieved with and without elective irradiation were compared for a number of different cancers. To do this the percent reduction in relapse rate resulting from elective radiotherapy was derived. This was calculated as (failure rate without radiotherapy – failure rate with radiotherapy)/(failure rate without radiotherapy). For example, if we use the example quoted earlier for head and neck cancer where the failure rate was 8% in electively irradiated patients compared with 35% in surgery-only patients, the 'adjusted' control rate would be (35–8)/35 = 77%. This method is preferred because the control rate that can be achieved with elective therapy will depend upon the level of control that is achieved in its absence. This is an important point in the design of clinical trials, since a greater number of patients would need to be accrued to achieve significant differences if the level of control without additional therapy is already high.

Adjusted control rates have been calculated for subclinical disease in patients with head and neck, breast, cervix, ovary, testis, lung carcinoma,

osteosarcoma, and melanoma. Total doses were normalized to equivalent 2-Gy fractions, the $LQED_2$, using a linear quadratic dose-effect model [9] and an α/β value of 15 Gy. The data showed a relationship between radiation dose and the control of subclinical disease that was compatible with the linearity expected from the model, and suggested that a dose of 20 Gy in 2-Gy fractions might reduce tumor survival by the order of 3 logs and increase control rates by about 20%.

The data were drawn from many diverse sources, and it would be wrong to overinterpret them. However, the curve appeared to intersect the abscissa at a dose of 6–15 Gy. Although in fact this may be zero, it is intriguing to speculate that an additional dose may be needed to control progressive growth of metastases during the time interval between surgery and irradiation, or to compensate for early, more rapid proliferation, although other explanations are possible. For example, small metastatic deposits of 1 to a few hundred cells may not be clinically relevant. Clearly these are important issues that need to be clarified in future studies. A similar analysis can be made for adjuvant chemotherapy.

In general, the limited data that are available suggest that the quantitative kinetics of subclinical disease can be represented by cells being shed in exponentially increasing numbers, and hence the distribution of metastases in patients being essentially log normal between 1 and 10^9 cells. Further, the evidence suggests that small metastases may be growing more rapidly with a lower cell loss factor than primaries, especially after surgery [3], which suggests that a short course of relatively aggresssive treatment and a minimum of delay may be a good general strategy. Clearly more studies are needed to validate these conclusions.

Conclusions

The conclusions from this study are: (1) Most metastatic disease is subclinical at the time of initial treatment and represents a wide range of cell numbers. (2) The dose-response relationship for control of subclinical metastases is more linear than threshold-sigmoid. (3) Biological effectiveness of adjuvant therapy should be measured as percent reduction in relapses with respect to the group not receiving treatment. This is not the same as clinical gain which depends on the number of initial recurrences. (4) Therapy that is suboptimal for the treatment of clinical disease can be effective against subclinical disease. (5) In situations where normal tissue tolerance is compromised, relatively low doses of therapy might still be effective. However, doses should not be reduced unless demanded by compromised tissue tolerance. (6) Adjuvant treatment should in

general be relatively aggressive, short in duration, and initiated as soon as possible after surgery.

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Treatment of the Neck in Head and Neck Mucosal Squamous Cell Carcinoma: What Our Experience Teaches

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The senior author feels highly honored at having been chosen to present this, the Second Annual del Regato Lectureship. Dr. Juan del Regato has been a leader in advancing the field of Oncology, developing Radiation Oncology as a separate specialty from Radiology, and organizing the members of the specialty under the American Society for Therapeutic Radiology and Oncology in the USA, and abroad under the International Society of Therapeutic Radiology and Oncology. As a teacher he has been devoted to his trainees, and has provided them with a broad clinical oncology background enriched with rotations through tumor pathology, surgical oncology and nuclear medicine, as well as enough time for their exposure to the existent practice of radiotherapy in other centers in the USA and Europe. He has trained over 100 radiation oncologists who themselves have become leaders in practice in areas around the world.

The topic for this lectureship is one that demanded Dr. del Regato's attention for all of his professional life. The senior author's familiarity with this subject is based on over 30 years of practice in Puerto Rico – an island with a high incidence of cancer of the oral cavity and pharynx – and his participation in the activities of the Radiation Therapy Oncology Group (RTOG) since it was founded in 1970. He has chaired the Group's Head and Neck Committee for 6 years and has been a member of it for over 20 years.

Table 1. Estimated new cancer cases per year [from 1]

Site	New cases/year
Buccal cavity	20,600
Pharynx	9,200
Larynx	12,600
Total	42,400

Table 2. Incidence of neck node metastasis by site [modified from 2]

Site	Range of metastasis, %
Oral cavity	5–65
Nasopharynx	56–90
Oropharynx	37–85
Hypopharynx	52–78
Larynx	1.5–64

Incidence of Head and Neck Mucosal Squamous Cell Carcinoma, and Factors Related to Lymph Node Metastasis

Carcinoma of the head and neck, an important component of the cancer problem in the USA and most other countries, has an incidence of new cases at least 5 times that of Hodgkin's disease [1]. Table 1 shows the predicted new cases for the year 1993 in this country; 42,400 new cases are expected to be diagnosed with carcinoma of the oral cavity, pharynx, or larynx, of which oral cavity will be the leading subsite. Moreover, Puerto Rico has shown the highest incidence of cancer of the oral cavity and pharynx in this hemisphere [2].

In a discussion of the head and neck mucosal cancer problem we must emphasize that this anatomic region encompasses 6 anatomical sites and 30 subsites, each developing tumors with characteristic clinical behaviors and lymph node metastatic problems, as well as responses to therapy [3]. The incidence of lymph node metastasis is intimately related to the site and stage of the primary disease. Table 2 shows the distribution of metastasis for the main sites in the head and neck region. In the oral cavity this ranges from 5% in the lower lip to 65% in the floor of the mouth. The highest incidence occurs in carcinoma of the nasopharynx (90%), followed by hypopharynx (78%), and the lowest occurs in carcinoma of the vocal cord (1.5–3%).

Table 3. Influence of low socioeconomic status on incidence of lymph node metastasis in base of tongue carcinoma

Institution	Positive nodes, %
Curie Institute [4]	67
M.D. Anderson [5]	70
Massachusetts General Hospital [6]	73
University of Puerto Rico[1]	85

[1] Lower socioeconomic status.

Table 4. N0 necks clinically but positive histologically [modified from 8]

Site	Histologically positive, %
Floor of mouth	40–50
Oral tongue	25–54
Base of tongue	22
Pharyngeal walls	66
Supraglottic larynx	16–26
Hypopharynx	38

Low socioeconomic status is related to a higher incidence of node metastasis (table 3), as it will affect the stage of the primary disease. In Puerto Rico, base of tongue cases have shown lymph node metastasis in 85%, but in more affluent populations such as in France and USA, lymph node metastasis occurs in 67–73% for this subsite. Poor differentiation of the tumor is another factor associated with high incidence of node metastasis in squamous cell carcinoma. Size of the primary tumor has been closely related to incidence of lymph node metastasis in the neck; the larger the primary lesion the higher the opportunity of developing lymph node metastasis. Type of spread of the primary tumor has also been related to nodal metastasis; the infiltrating variety has higher chances of developing positive nodes than the superficial, non-infiltrating type.

Patients may show metastatic nodes in the neck when they present initially (table 2), sometimes as the initial manifestation of the disease [7], or they may show them in the surgical specimen when submitted to elective neck dissection in the absence of palpable nodes (N0) (table 4). Patients who are initially stage N0 but are not submitted to elective neck dissection may develop metastatic

Table 5. Conversion of N0 into N+ [modified from 3]

Site	Conversion, %
Lip	3–9.6
Buccal mucosa	16
Gingiva	17
Retromolar	10–15
Hard palate	22
Floor of mouth	20–35

neck nodes during the period following treatment of the primary tumor, with a conversion rate ranging from 10 to 15% in the anterior tonsillar pillar/retromolar trigone area to 50% in the nasopharynx. The conversion rates in the oral cavity are shown in table 5. Both cervical node chains are at risk of metastasis when the primary tumor extends across the midline. However, unilateral lesions such as tonsillar fossa tumors may have a 7–8% chance of contralateral metastasis, particularly when the base of tongue is invaded, even though the lesion may be located far from the midline. In some sites, such as nasopharynx and base of tongue, 50% of the cases may show bilateral palpable nodes at the time of diagnosis.

Detection of Clinically Positive Lymph Nodes and Staging

Traditionally we have employed physical examination for the identification of clinically positive lymph nodes in the neck, and the data in this report are based on palpable nodes. In recent years, CT and MRI have been added for this purpose, and are presently required for the evaluation of cervical lymph nodes in all RTOG head and neck cancer studies. In thin patients, adequate palpation can detect small nodes, but in the obese short-necked person, palpation may be imprecise and imaging is often a better method. The RTOG requires that when N+ status is based on the presence of nodes found only on CT or MRI scans (not palpable on clinical examination), the size of the node so detected must be 1 cm or bigger in its minimal axial diameter, or contain necrotic regions regardless of size.

The correlation of clinical nodal status with histologic proof can be seen in table 6. When the nodes were palpable but clinically insignificant, all of 12 needle biopsies were histologically negative, but 99% of 164 biopsies on N3 nodes were histologically positive. The presently accepted staging system for metastatic neck lymph nodes can be seen in table 7.

Table 6. Histological proof of metastasis [from 9]

Nodal status	Needle biopsies	Histology positive	
		n	%
Palpable, not significant	12	0	0
N1–2	135	129	95
N3	164	163	99
All	311	292	94

Table 7. Regional lymph node staging (N) neck

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest diameter
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Management of the Neck in Patients with no Palpable Lymph Nodes (N0)

When the primary tumor is managed surgically, elective neck dissection is frequently performed on N0 patients with high (over 15%) probability of histologic tumor in the nodes. The probability that a clinically negative neck shows histologically positive nodes, if an elective neck dissection is practiced, can be seen in table 4. This could be 50% or higher in the floor of the mouth, oral tongue and pharyngeal wall lesions. After an elective node dissection has been performed, the possibility of reactivation of the disease in the neck still

exists even in patients who had no histologic evidence of tumor: in a group of 160 such patients, 11 (7%) recurred in the neck [4]. Among 51 N0 patients with minimal histopathologic evidence of node metastasis, 14% (7/51) showed recurrence. In 33 patients with major histopathological evidence of node metastasis, 21% had neck recurrence even though postoperative irradiation was given.

When the primary tumor is managed by radiotherapy in N0 cases, a common practice is to extend the irradiation fields to include the pertinent lymph node areas. Usually the fields of irradiation extend caudally to the clavicle, anteriorly and posteriorly to encompasss the jugular and posterior cervical nodes, and superiorly to cover the primary tumor, its extensions and the pertinent upper cervical and parapharyngeal nodes. The elective irradiation dose to the lymph nodes will range from 4,500 to 5,000 cGy at the rate of 180–200 cGy/fraction, 5 times/week, with photon energies of 6 MEV or lower. A compensator may be required to assure adequate radiation dose for nodes located immediately under the skin. The spinal cord dose should preferably not exceed 4,000 cGy. Additional lymph node irradiation, beyond the 4,000-cGy photon dose level, can be administered with electron beam.

The success rate of prophylactive elective neck irradiation exceeds 95% freedom from evolution into N+ status. In the RTOG split-course study, in 109 patients with carcinoma of the nasopharynx, tonsillar fossa and base of tongue with no palpable nodes initially and the primary tumor controlled by subsequent radiotherapy, the freedom from tumor in the irradiated neck by the fifth year was 98%. In 724 N0 cases reported from the Curie Institute in Paris, 13 (1.8%) failed in the nodes only by the end of the second year [4]. Over 80% of failures should be evident by the end of the second year after treatment.

Management of the Clinically Positive Cervical Lymph Node Metastasis

The management of neck metastasis from an unknown primary is covered by Dr. Fu in this volume. Based on our past experience with this clinical problem, our present policy is to limit the irradiation volume in these patients to the minimum required by the nodal problem, to preserve good quality of life [10].

In cases with known primary site, the management of the clinically positive lymph node metastasis is closely related to the management of the primary tumor. Since the chances of finding positive histology in significant clinically positive neck lymph nodes is close to 100% (table 6), we do not need to biopsy these nodes to proceed with therapy. When surgery is used for the primary

tumor, lymph node dissection is usually performed for the palpable cervical lymph node(s). Surgery can be of the nature of a modified neck dissection, with or without irradiation, as promoted at the MD Anderson Cancer Center by Jesse [11], or a classical neck dissection as developed at Memorial Sloan Kettering Cancer Center [12].

After neck dissection for clinically positive nodes, approximately one fourth of patients will recur in the neck. In a collation of results from the medical literature, Shimm [13] found an average postsurgical recurrence rate of 24% (350/1,464), ranging from 12 to 48% and with a median of 23%. Neck recurrence is more common in nodes with extracapsular invasion or fixation, size >3 cm, multiple or different levels of involvement, and large associated primary tumors. Strong [14] reported a 70% incidence of neck recurrence in patients who were found to have positive nodes at multiple levels if they had surgery only.

When the primary lesion is managed by radiotherapy, most of the clinically significant palpable nodes are in the path of the beam, and thereby receive the dose that is considered adequate for the primary lesion and the adjoining areas. Adjacent nodal areas with no palpable nodes should receive radiation doses considered adequate for the N0 cases.

The usual irradiation of these cases consists of teletherapy with photon energy of 1–6 MEV from a cobalt teletherapy unit or a linear accelerator. Lateral opposing fields are used for the upper part of the neck and the primary tumor, and an anterior field is used for the lower neck. Adequate protection should be provided to the salivary glands whenever possible, to the larynx when irradiation to this area is unnecessary, and to the spinal cord. As previously stated for N0 stage, nonpalpable nodes will receive an approximate dose of 4,500–5,000 cGy with fractions of 180–200 cGy, 5 days/week; palpable nodes will receive at least 7,000 cGy.

Results of Radiotherapy

The results of radiotherapy in the management of cervical lymph node metastasis can be expressed in terms of complete nodal clearance of palpable neck nodes after irradiation, long-term control of neck metastasis, and survival. In the case of postoperative radiotherapy, success is achieved when the patient continues free of reactivation of the tumor in the neck. The time for complete regression of tumor in lymph nodes after radiotherapy is variable: some nodes disappear by the end of radiotherapy but some may take months to regress. Bataini [16] reported clinical complete response of only 32% by the end of radiotherapy, but 76% 2 months afterwards ($p<0.0001$) (table 8).

Table 8. Regression of neck node metastases and time after radiotherapy (RT) [modified from 16]

Time for evaluation	Cases, n	Complete response, %
At end of RT	759	32
Two months after RT	546	76
		$p < 0.00001$

Table 9. Nodal clearance in 175 N+ patients with T controlled [from RTOG split-course study]

Stage	Cases, n	N cleared, %
T1–2	43/50	86
T3	66/76	87
T4	36/49	73
All T-N+	145/175	83
N1–2	81/86	94
N3	64/89	72
		$p < 0.001$

N+ = Clinically positive nodes; T = primary tumor.

The probability of achieving N clearance with different T and N stages in the mentioned RTOG split-course study is shown in table 9. When the primary tumor was controlled, 83% of clinically positive nodes disappeared with radiotherapy; this ranged from 86% for patients with T1–2 primaries to 73% in T4 lesions. In N1–2 stages 94% were controlled with radiotherapy, versus 72% in N3 necks ($p < 0.001$). The probability of first failure in the neck by the fifth year, in patients who achieved complete response in both the primary and nodal areas, can be observed in table 10. This ranged from 4% in N0 patients to 8% in N+ patients. The survival achieved with radiotherapy related to nodal status, based on 401 patients in the RTOG split-course study, can be observed in table 11. The 5-year survival diminishes with advancing N stage. N0 cases showed more than a 2-fold greater 5-year survival than patients with positive nodes.

Table 10. Estimated probability of first failure in the neck by 5 years in patients achieving complete disappearance of tumor in primary and nodal areas [from RTOG split-course study]

N stage	Estimated probability, %
0	4
All N+	8
N1	8
N2	6
N3	8

Table 11. Nodal status and survival based on 401 patients with carcinoma of tonsillar fossa, nasopharynx, and base of tongue

Nodal stage	Survival rates, %	
	3 years	5 years
N0	51	44
N1–2	33	26
N3	23	17

A number of factors have been identified as being of possible influence in the control of neck lymph metastasis by radiotherapy in the RTOG experience. Control of the primary tumor is the leading one. N stage, radiation dose, size of the node, and elapsed treatment days during radiotherapy have also been found important. The last is a clinically modifiable condition: prolongation of elapsed treatment time of 2 weeks or longer can reduce control of tumor and survival ($p = 0.007$ and 0.01) [15]. This experience has also been shared by Bataini [16] at the Curie Institute. Uncompensated interruptions during the course of radiotherapy of 5 days or more can also reduce locoregional control and survival ($p \leq 0.03$) [17]. However, T stage, site of the primary tumor, sex, age, differentiation of the tumor, and type of fractionation lose importance when one corrects for response of the primary tumor. The significance of concomitant chemotherapy has not been completely defined; however, in the Intergroup Study 0034 [18] sequential chemotherapy (using cisplatin and 5-FU) and

Table 12. Factors favoring the use of salvage surgery

Node size > 3 cm
Residual palpable nodes, regardless of size
Prolongation of therapy longer than 2 weeks
Insufficient radiation dose
Fixation of node prior to radiotherapy (invasion of capsule)
Multiple nodes
Large primary tumor

postoperative radiotherapy seemed to reduce the incidence of first failure in the neck versus radiotherapy alone (10 vs. 5% $p = 0.03$). The group's experience with a pilot study of concurrent cisplatin chemotherapy and radiotherapy for advanced inoperable cases gave promising results [19], which provided the basis for an ongoing randomized trial in patients with advanced carcinoma of the nasopharynx. Continuation of the smoking habit during radiotherapy has been associated with lower tumor response and survival than patients who do not smoke [20].

Salvage Surgery after Radiotherapy

After radiotherapy for lymph node metastasis in the neck, a number of patients will require a surgical salvage procedure [21]. There is no unanimity of opinion as to which patients should be submitted to surgery but some factors favor its use (table 12). Some centers favor surgery on all patients with initially palpable nodes measuring 3 cm or larger regardless of response, but many institutions including ours and others in the RTOG limit surgery to residual palpable tumor. Needless to say, the larger the node the higher the chances of having residual palpable tumor. Bataini et al. [22] reported that 169 patients with oropharyngeal and pharyngolaryngeal lesions and nodes of 5–10 cm diameter had 20% failure, versus 7% in 1,646 patients with nodes of 5 cm or smaller. This surgery can be limited to an adenectomy, or can be a more extensive procedure. In a recent publication by Horiot et al. [23], 3% of patients had adenectomy alone; of 9 such cases residual disease was found in 3. In programming surgery, one should keep in mind the slowness of regression of some of these tumors, as shown by Bataini [16]. Salvage surgery for the cervical lymph nodes has added from 5 to 6% CR to the value achieved by radiotherapy only in various studies of the RTOG.

Pre- or Postoperative Radiotherapy

Preoperative irradiation is a viable alternative for patients with metastatic nodes of questionable operability. A preoperative dose of 5,000 cGy at the rate of 200 cGy/day was tolerated well in one of the RTOG studies [24] with no increase in surgical complications. Nodes of questionable mobility can be made operable by such management. Fixed nodes are best managed initially by radiotherapy, and if they become operable then surgery is performed [11].

Postoperative irradition should be offered to all patients whose surgical pathology findings denote a high chance of recurrence in the neck. Nodes 3 cm or larger, nodal capsule invasion [4], presence of nodes at multiple levels [14], and any degree of fixation should be submitted to postoperative neck irradiation. The usual dose for postoperative irradiation in the RTOG has been 5,000 cGy in 5–6 weeks with fractions of 180–200 cGy/day, 5 days/week to all the neck areas, boosting the areas of previous tumor to 6,000 cGy. At the Curie Institute [4] the additional dose has ranged from 1,500 to 2,000 cGy to areas of nodal capsule invasion.

Arriagada et al. [25] found that in patients with hypopharyngeal and laryngeal lesions with all N stages, lymph node recurrence at 2 years was 14% (8/57) with postoperative doses of 4,500 cGy or higher, versus 50% (25/50) with doses $<4,500$ cGy pre- or postoperatively. The interval between surgery and the initiation of postoperative irradiation is critical. Intervals longer than 6 weeks are associated with reduced curability [26].

The Impact of Cervical Lymph Node Metastasis on Control of the Primary Tumor by Radiotherapy, Incidence of Distant Metastasis and Survival

The presence of cervical lymph node metastasis is known to correlate with various parameters, including control of the primary tumor by radiotherapy, incidence of distant metastasis, and survival. The influence of nodal status on primary tumor response to radiotherapy can be observed in table 13, which is based on 3,031 patients from the RTOG database. Within each T stage the primary tumor response declines with advancing N stage. T1 N0 cases showed 92% CR versus 71% for T1 N3.

The impact of cervical node metastasis on distant metastasis can be observed in table 14 showing data based on 231 patients who achieved CR in the RTOG split-course study. N0 patients showed 13% distant metastasis as first failure by the fifth year versus 30% when the nodes were positive. Using a larger patient sample of 2,648 cases from the RTOG database, Leibel et al. [27]

Table 13. Influence of neck node metastasis on primary tumor response based on 3,031 patients in the RTOG database

T stage	Complete response of primary disease, %			
	N0	N1	N2	N3
T-1	92	81	87	71
T-2	83	73	70	56
T-3	70	61	63	50
T-4	64	45	44	38

Table 14. Influence of N stage on distant metastasis at 5 years in 231 patients with complete response of T and N [from RTOG split-course study]

Stage	Probability of distant metastasis as first failure at 5 years, %
N0	13
N+	30
N1	25
N2	29
N3	33
All patients with CR	24

showed similar findings for N0 and N1 patients, but N2 and N3 lesions showed much higher (43 and 46%) distant metastatic rates. They also stated that the distant metastatic rate is lower when locoregional control is achieved versus when locoregional failure is present.

The influence of nodal status on survival is shown in table 11, presenting 3- and 5-year survival rates in 401 patients in the RTOG split-course study. N0 patients showed 44% 5-year survival versus 17% for N3. Fitzpatrick and Tepperman [28] reported on carcinoma of the floor of the mouth with positive nodes (226 patients): if the nodes were controlled 33% of 69 patients lived 5 years, versus 17.5% of 157 patients if the nodes were uncontrolled.

Conclusions

To conclude:

(1) Mucosal squamous cell carcinomas of the upper air and food passages ('head and neck') develop in a diversity of sites (6) and subsites (30), accounting for their great variability in clinical behavior.

(2) Overall, 50% of these lesions will develop metastasis to cervical lymph nodes. This rate varies with the primary site from less than 5% in the lower lip and vocal cord to 85% in the base of the tongue.

(3) Cervical metastases may be evident at diagnosis, in elective neck dissection specimens, or after treatment of the primary during observation. The conversion rates vary considerably from 10 to 50%, depending on the site and stage of the primary disease.

(4) Management for the nodes should be closely related to that for the primary. When surgery is used for the primary, it is usually extended to treat the neck for clinically positive nodes, and for clinically negative but high-risk nodes.

(5) After dissection, the choice of postoperative radiotherapy should depend on the histologic findings in the neck specimen: >3 cm nodal size, capsular invasion, fixation, multiple nodes, multiple levels.

(6) Postsurgical recurrences range from about 25% of cases with clinically positive nodes to about 7% of those with both clinically and histologically negative nodes. Postoperative irradiation will reduce these to less than half the expected rates, if doses of 4,500 cGy or higher (6,000 or higher to the area of previous tumor) are used in 180–200 cGy daily fractions.

(7) When radiotherapy is used for the primary lesion, the fields usually encompass the neck areas with palpable nodes or with high risk of occult disease, and give 4,500–5,000 cGy. Therapeutic doses for positive nodes approach those for the primary tumor of 7,000 cGy.

(8) Neck irradiation can help preserve N0 status in 98% of necks when the primary lesion has been controlled. Similarly, clinically positive nodes can be controlled by radiotherapy alone in overall 83% of cases (94% of N1–2 cases) with controlled primary lesions. Reappearance of tumor occurs in fewer than 10% of completely responding cases over 5 years.

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Neck Node Metastases from Unknown Primary

Controversies in Management

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Neck node metastasis from unknown primary is an infrequent but challenging problem encountered by the head and neck surgeon and radiation oncologist. The frequency of neck node metastases from unknown primary, relative to the total number of neoplasms of the aerodigestive tract, varies from 3 to 9% with an average of 5% [1]. Although there have been numerous papers written about this subject, the management of a patient with a neck node metastasis from an occult primary site remains controversial. In this presentation, I will attempt to address some of the common issues concerning this topic. Specifically, I will focus my discussion on metastatic squamous cell carcinoma in the upper and/or middle neck, which most likely originates from a primary site in the head and neck region rather than from an infraclavicular primary.

How Should Pathological Diagnosis of a Neck Node Suspicious for Metastasis from an Occult Primary Be Obtained – Fine Needle Aspiration or Open Biopsy?

The first and most important step in the diagnostic evaluation of a neck node suspicious for neoplasm with no apparent primary site, after a careful history and physical examination, is to establish the pathological diagnosis.

A fine needle aspiration biopsy (FNA) is the most expeditious procedure; no hospitalization or anesthesia is required. Tumor seeding is rare, and in the

hands of an experienced pathologist the diagnostic accuracy is high [2]: in a series of 151 patients who presented with cervical node metastases from unknown primary, FNA was sufficient to reach a diagnosis in 136 (90%) of the patients [3]. Compared with open biopsy, the FNA technique causes less tissue disturbance, carries a lower morbidity, and is less expensive. However, when multiple FNAs fail to provide a definitive pathological diagnosis, an open biopsy becomes necessary.

Does Open Biopsy Adversely Affect the Prognosis?

For many years, it has been a dictum of head and neck surgeons that an open biopsy should not be done unless the surgeon is capable of, and prepared to perform a radical neck dissection should the frozen section indicate epidermoid carcinoma or melanoma. McGuirt and McCabe [4] showed that the incidences of wound necrosis, neck recurrence and distant metastasis were higher in patients having biopsy before definitive treatment than in patients having biopsy at the time of definitive treatment or having no biopsy. The definitive treatment consisted of radical neck dissection with or without resection of the primary tumor. However, recent studies suggest that open biopsy of neck nodes does not adversely affect the prognosis when adequate treatment, which usually includes radiotherapy, is given subsequently [5, 6].

What Imaging Studies Should Be Performed, Computed Tomography or Magnetic Resonance Imaging, and When?

Both computed tomography (CT) and magnetic resonance imaging (MRI) are useful in the diagnostic staging evaluation of head and neck cancer. MRI provides excellent soft tissue contrast resolution and is most useful for evaluating soft tissue neoplasms, especially when there is muscle infiltration. CT is most useful in detecting subtle osseous changes. In a patient with an occult primary tumor, the role of the CT or MRI scan is to identify the location of the occult primary tumor, suggest suspicious areas for tissue biopsy during endoscopy, detect occult lymph node metastasis in the ipsilateral or contralateral neck (which may not be clinically palpable), and further assess the extent of nodal disease [7]. The choice of which study to use depends on the clinical questions in each patient, the relative cost and the level of patient cooperation. If a primary in the nasopharynx is

suspected, high-resolution MRI is more accurate in evaluating the nasopharynx than CT, especially for early tumors that may not yet have infiltrated the fat planes deep to the mucosal surface. On the other hand, CT may be preferable to MRI in evaluating the larynx and hypopharynx in a patient who has rapid breathing or coughing and is unable to cooperate for MRI examination. CT and contrast-enhanced MRI in combination with fat suppression techniques are probably equally effective in detecting occult neck nodes. MRI is superior to CT in detecting tumor invasion of the carotid artery. However, CT is less expensive than MRI. Regardless of which imaging study is chosen, it is important that the CT or MRI scans be performed prior to biopsy, since biopsy can cause soft tissue changes that may be difficult to interpret.

What Other Laboratory Studies May Be Helpful in Establishing the Primary Site?

A chest x-ray should be performed to rule out primary or metastatic lesions in the chest. In addition, anti-Epstein-Barr virus (EBV) antibody titers – specifically, IgA anti-viral capsid antigen (VCA), and the detection of EBV genomes in neck node metastases by polymerase chain reaction [8] or in situ hybridization [9] may be helpful in establishing an occult primary site in the nasopharynx.

Nasopharyngeal carcinoma has been closely associated with EBV, particularly in patients with undifferentiated or nonkeratinizing carcinomas. Elevated IgA anti-VCA antibody titer is found in 69% of North American patients with nasopharyngeal carcinoma compared with 9–15% of patients with benign or other malignant head and neck tumors and normal controls [10]. Although the presence of EBV genome or EBV nuclear antigen in the neck nodes per se does not necessarily indicate a nasopharyngeal primary, detection of positive EBV genome in the metastatic lymph node coupled with elevated IgA anti-VCA antibody titer would be strongly suggestive of a primary in the nasopharynx.

What Additional Surgical or Diagnostic Procedures Are Needed to Establish the Primary Site?

When an occult primary in the upper aerodigestive tract is suspected, examination under anesthesia with panendoscopy should be carried out. It is important to palpate the potential occult primary sites such as the base of tongue, the tonsil, and the fossa Rosenmuller. 'Directed' biopsies of the base of

tongue, tonsil, pyriform sinus and nasopharynx, as well as any areas suspicious on visualization, palpation or MRI or CT scans, should be performed.

If the Primary Remains Unknown after Appropriate Diagnostic Evaluation Work-up, What Are the Treatment Options?

Treatment options for neck node metastases from unknown primary consist of surgery or radiotherapy alone, or combined surgery and radiotherapy. Radiotherapy may be delivered to the involved neck only or to the neck and potential primary sites in the mucosa. Chemotherapy has been used in combination with radiotherapy and/or surgery for advanced neck disease [11].

What Are the Options and Results of Surgery Alone?

Surgical options in the treatment of metastatic neck node(s) from unknown primary include radical neck dissection or modified radical neck dissection. Bilateral neck dissections, usually staged, are performed for bilateral positive neck nodes.

The type of neck dissection to be performed has been controversial. Lefebvre et al. [3] noted a significant difference ($p<0.01$) in the neck recurrence rate between patients who underwent radical neck dissection (15%) and those who had modified neck dissection (25%). The neck recurrence rate was 42% in patients who underwent excisional biopsy only and 54% in patients who had incisional biopsy followed by neck dissection. All patients also received radiotherapy to the neck. However, Carlson et al. [20] noted no significant correlation between the incidence of treatment failures and the type of surgical procedure performed in 93 patients with cervical metastases from an unknown primary who received radiotherapy to the neck only, or neck plus nasopharynx and oropharynx, or neck plus nasopharynx, oropharynx and hypopharynx.

Although a modified neck dissection can be performed in patients with small mobile nodes without loss of regional control, a standard radical neck dissection has been used in the majority of patients with neck node metastases from unknown primary.

Table 1 shows the results of selected series using surgery alone for neck node metastases from unknown primary. The proportion of patients with stage NX (node excised with no gross residual disease) or N1 disease ranged from 33 to 87% [12–17]. The ipsilateral neck failure rate ranged from 8 to 25%, and the contralateral neck failure rate ranged from 4 to 16%. Although no treatment was given to the potential occult primary sites in the mucosa, a subsequent

Table 1. Neck node metastases from unknown primary: results of surgery alone

Reference	Patients n	Stage NX[a]-1/N2-3 n (%)	Ipsilateral neck failure, n (%)	Contralateral neck failure, n (%)	Subsequent 1° above the clavicle, n (%)	Survival %
Coster (1992) [12]	24	13 (54)/11 (46)	6 (25)	2 (8)	1 (4)	66 (5-year actuarial)
Wang (1990) [13]	57	37 (65)/20 (35)	7 (12)	NA	7 (12)	86 (5-year actuarial cause-specific)
Leipzig (1981) [14]	8	7 (87)/1 (12)	NA	NA	9/32 (28) of total series	25 (3-year absolute)
Nordstrom (1979) [15]	12	4 (33)/8 (67)	NA	NA	1/51 (2) of total series	42 (5-year absolute)
Coker (1977) [16]	26	9 (35)/17 (65)	2 (8)	1 (4)	4 (15)	68 (5-year NED)
Jesse (1973) [17]	104	44 (42)/60 (58)	25 (24)	16/97 (16)	21 (20)	57 (3-year NED)
Total	231	114/231 (49)/ 117/231 (51)	40/211 (19)	19/147 (13)	33/211 (16)	

NA = Not available; NED = no evidence of disease.
[a] NX = Node excised with no gross residual disease.

primary above the clavicle was detected in only 4–20% of the patients. Survival was related to the N-stage and ranged from a 3-year absolute survival of 25% [14] to a 5-year actuarial cause-specific survival of 86% [13].

Although control of the neck disease can be achieved with surgery alone in patients with early stage disease, most series show an improved neck control rate with combined surgery and radiotherapy for more advanced neck disease.

If Radiotherapy Is Selected, Should the Treatment Volume Include the Involved Neck Only, or the Involved Neck and the Potential Occult Primary Sites? What Are the Results of Radiotherapy?

As shown in tables 2 and 3, the majority of patients who received radiotherapy with or without a neck dissection (RT ± S) had more advanced neck disease compared with patients treated with surgery alone [3, 13–26]. In the radiotherapy groups, the proportion of patients who also had neck dissec-

Table 2. Neck node metastases from unknown primary: results of radiotherapy (RT) ± surgery (S) to *ipsilateral* neck and mucosa

Reference	Patients n	Stage NX[a]-1/N2-3 n (%)	Ipsilateral neck failure, n (%)	Contralateral neck failure, n (%)	Subsequent 1° above the clavicle, n (%)	Survival %
Marcial-Vega (1990) [18]	19	7 (37)/12 (63)	10 (53)	0	1 (5)	37 (5-year actuarial)
Glynne-Jones (1990) [19]	58[b]	8 (14)/50 (86)	17 (29)	1 (2)	6 (10)	40 (5-year actuarial)
Carlson (1986) [20]	20[c]	NA	2 (10)	2 (10)	3 (15)	71 (10-year determinate)
Leipzig (1981) [14]	8 RT	5 (63)/3 (37)	NA	NA	9/32 (28) of total series	38 (3-year absolute)
	16 RT+S	2 (13)14 (87)/	NA	NA		50 (3-year absolute)
Fitzpatrick (1974) [21]	95	NA	NA	NA	8 (8)	32 (5-year actuarial) 43 (5-year actuarial of the 68 patients who received ≥ 45 Gy)
Total	216	22/101 (22)/ 79/101 (78)	29/97 (30)	3/97 (3)	18/192 (9)	

NA = Not available.
[a] NX = Node excised with no gross residual disease.
[b] Nine had RT to bilateral neck.
[c] Seven had RT to bilateral neck.

tion or excisional biopsy ranged widely from 6 to 90% in patients who received radiotherapy to the ipsilateral neck and sometimes mucosa (ipsilateral RT ± S), and from 35 to 92% in patients who received radiotherapy to bilateral neck and mucosa (bilateral RT ± S).

There is no significant difference in either ipsilateral or contralateral neck failure rates between the ipsilateral versus bilateral RT ± S groups (tables 2, 3): ipsilateral neck failure occurred in 10–53% of the patients receiving ipsilateral RT ± S, and in 3–57% of the patients receiving bilateral RT ± S. The contralateral neck failure rates were low in both groups.

Table 3. Neck node metastases from unknown primary: results of radiotherapy (RT) ± surgery (S) to *bilateral* neck and mucosa

Reference	Patients n	Stage NX[a]-1/N2-3 n (%)	Ipsilateral neck failure, n (%)	Contralateral neck failure, n (%)	Subsequent 1° above the clavicle, n (%)	Survival %
Maulard (1992) [22]	113	30 (27)/83 (73)	16 (14)	NA	8 (7)	38 (5-year actuarial)
Marcial-Vega (1990) [18]	53	5 (9)/48 (91)	30 (57)	3 (6)	8 (15)	39 (5-year actuarial)
Harper (1990) [23]	69[b]	18 (26)/51 (74)	14 (22)	0 (0)	8 (12)[c]	48 (5-year actuarial)
Wang (1990) [13]	56 RT	29 (52)/27 (48)	16 (29)	NA	3 (5)	74 (5-year actuarial cause-specific)
	44 RT+S	11 (25)/33 (75)	10 (23)	NA	5 (11)	63 (5-year actuarial cause-specific)
Lefebvre (1990) [3]	98[d]	NA	20 (20)	4 (4)	25/180 (13) of total series	35 (5-year actuarial)
Bataini (1987) [24]	90 RT	16 (18)/74 (82)	46 (51)	NA	6/138 (4) of total series	22 (5-year absolute)
	48 RT+S	29 (62)/18 (38)	8 (17)	NA	6/138 (4) of total series	55 (5-year absolute)
Carlson (1986) [20]	73	NA	2 (3)	0 (0)	5 (7)	70 (10-year determinate)
McCunniff (1986) [25]	19	12 (63)/7 (27)	7 (37)	0 (0)	2 (11)	61 (3-year NED)
Silverman (1983) [26]	83	34 (41)/49 (59)	29 (35)	NA	13 (16)	38 (5-year actuarial)
Nordstrom (1979) [15]	17 RT	1 (6)/16 (94)	NA	NA	1/51 (2) of total series	24 (5-year absolute)
	22 RT+S	3 (14)/19 (86)	NA	NA		27 (5-year absolute)
Coker (1977) [16]	16 RT	0 (0)/13 (100)	5 (31)	0 (0)	0 (0)	16 (5-year NED)
	14 RT+S	4 (33)/8 (67)	5 (36)	2 (14)	4 (29)	50 (5-year NED)
Jesse (1973) [17]	52 RT	11 (21)/41 (79)	11 (21)	0 (0)	3 (6)	48 (3-year absolute DFS)
	28 RT+S	6 (22)/22(78)	4 (14)	0 (0)	4 (14)	47 (3-year absolute DFS)
Total	895	209/718 (29)/ 509/718 (71)	223/856 (26)	9/422 (2)	63/620 (10)	

NA = Not available; NED = no evidence of disease; DFS = disease-free survival.

[a] NX = Node excised with no gross residual disease.

[b] Four patients received RT to the neck only.

[c] Five (8%) in field; 3 (4%) out of field.

[d] Treated curatively out of a total of 190 patients.

Fu

A subsequent primary above the clavicle was detected in 5–15% of patients who received ipsilateral RT ± S, and in 0–29% of patients who received bilateral RT ± S. There was also no significant difference in the rate of detection of subsequent primary above the clavicle between these two groups.

Survival appeared to be related to the stage of the neck disease and ranged from a 5-year actuarial survival of 32% [21] to a 10-year determinant survival of 71% [20] in patients receiving ipsilateral RT ± S. In patients who received bilateral RT ± S, the survival ranged from a 22% 5-year absolute survival [24] to a 74% 5-year actuarial cause-specific survival [13].

As noted, the proportion of patients who also received surgery to the neck varied from series to series. The results of patients treated with radiotherapy alone and radiotherapy combined with surgery were analyzed separately in only 6 series [13–17, 24]. Only the series by Bataini et al. [24] showed a significantly lower ipsilateral neck failure rate and improved 5-year survival rate in patients who received the combined treatment. However, this may be a reflection of patient selection and a greater proportion of patients with advanced neck disease in the radiotherapy-alone group. Some of the patients who received radiotherapy alone were irradiated palliatively.

From the data available, it appears that the results of ipsilateral RT ± S and bilateral RT ± S are similar. It should be noted that in the majority of patients who received radiotherapy to the ipsilateral neck, at least the ipsilateral mucosa was also included in the irradiated volume [14, 19, 21]. However, the patient population, radiotherapy techniques and total doses were quite variable among the different series and the results are not strictly comparable.

Compared with surgery alone, irradiated patients appeared to have a lower incidence of contralateral neck failure and subsequent primary above the clavicle, although the incidence of ipsilateral neck failure was higher in the irradiated patients, largely due to the greater proportion of patients with more advanced neck disease.

Is There a Role for Chemotherapy?

Chemotherapy has seldom been used in the primary treatment of patients with neck node metastases from unknown primary. In the past, chemotherapy was administered primarily for palliation of patients with advanced or recurrent neck disease. However, a recent report by de Braud et al. [11] suggests improved complete response and median survival rates in patients receiving chemotherapy and radiotherapy ± surgery for advanced metastatic squamous cell carcinoma localized to the neck from an unknown primary. In their experience, although there was a greater proportion of patients with N3 disease

in the combined chemotherapy and radiotherapy group than the radiotherapy-alone group (75 vs. 56%), the complete response rates (81 vs. 37%) and median survival rates (38 vs. 10 months) were greater in the combined treatment group. Chemotherapy consisted of cisplatinum used concurrently with radiotherapy or cisplatinum and 5-FU as an adjuvant before or after radiotherapy ± radical neck dissection. However, the total number of patients who received chemotherapy was small (16 patients). At the present time, the role of chemotherapy in the management of patients with metastatic neck nodes from unknown primary has not been established.

What Are the Most Common Subsequent Primary Sites above the Clavicle? Does Discovery of the Subsequent Primary Site Affect the Prognosis?

Subsequent primary above the clavicle was detected in a total of 155/1,424 (11%) of the patients from 16 series (table 4). The most common subsequent primary sites were in the oropharynx (base of tongue or tonsil), oral cavity, and hypopharynx (mostly pyriform sinus). The high incidence of subsequent primary sites in the oral cavity was probably due to the exclusion of oral cavity in the radiation fields in most series.

Data on the salvage rates of a subsequent primary above the clavicle were available in eight series [3, 17, 19, 20, 22, 23, 25, 26]. Salvage treatment usually by surgery was attempted in 92/98 (94%) of the patients whose primary site was subsequently detected above the clavicle, and was successful in 39/92 (42%) of the patients who underwent a salvage attempt. There was no significant difference in survival between patients whose subsequent primary was found and those whose primary was not found [14, 18, 22].

Comments and Conclusions

Management of metastatic neck nodes from unknown primary remains a challenge to head and neck oncologists. Treatment selection depends on node size, number, location, histological differentiation, and the patient's age and general condition. A single node $\leq$3 cm in diameter in the submandibular region usually arises from a primary in the oral cavity, which can be detected early and treated with either surgery or radiotherapy [27]. Neck dissection is the preferred treatment in this situation. Single nodes $\leq$3 cm in diameter in other locations in the neck can be treated with either a radical neck dissection or radiotherapy alone. Radiotherapy is the preferred treatment for patients who

Table 4. Sites of subsequent 1° above the clavicle and salvage rate

Reference	Subsequent 1° above the clavicle n (%)	Subsequent 1° sites						Salvage rate n salvaged/ n attempted (%)
		oro-pharynx	hypo-pharynx	naso-pharynx	larynx	oral cavity	others	
Maulard (1992) [22]	8/113 (7)	3	1	0	1	3	0	2/7 (29)
Coster (1992) [12]	1/24 (4)	0	0	0	1	0	0	NA
Wang (1990) [13]	15/157 (10)	4	0	2	2	7	0	NA
Marcial-Vega (1990)[18]	9/72 (13)	4	3	1	0	1	0	NA
Glynne-Jones (1990) [19]	6/58 (9)	0	0	4	1	0	1	2/6 (33)
Harper (1990) [23]	8/69 (12)	2	0	1	2	3	0	2/5 (40)
Lefebvre (1990) [3]	25/180 (13)	NA	NA	NA	NA	NA	NA	4/25 (16)
Bataini (1987) [24]	6/138 (4)	2	3	0	0	0	1	NA
Carlson (1986) [20]	8/93 (9)	1	0	1	0	4	2	6/8 (75)
McCunniff (1986) [25]	2/19 (11)	1	0	0	0	1	0	0/0
Silverman (1983) [26]	13/83 (16)	3	2	0	2	4	2	7/13 (54)
Leipzig (1981) [14]	9/32 (28)	3	2	4	0	0	0	NA
Nordstrom (1979) [15]	1/51 (2)	0	0	0	1	0	0	NA
Coker (1977) [16]	8/56 (14)	2	1	1	3	1	0	NA
Fitzpatrick (1974) [21]	8/95 (8)	2	2	2	2	0	0	NA
Jesse (1973) [17]	28/184 (15)	9	8	2	2	4	3	16/28 (58)
Total	155/1,424 (11)	36	22	18	17	28	9	39/92 (42)

NA = Not available.

are unreliable for close follow-up. On the other hand, surgery is preferred for young patients and for elderly patients who have poor tolerance of radiotherapy. However, if surgery is chosen, postoperative radiotherapy is indicated when there is known residual disease, extracapsular spread, involvement of more

than one node, soft tissue involvement, perineural and/or vascular invasion, or poorly differentiated histopathology.

If radiotherapy is chosen, then elective irradiation of at least the ipsilateral potential occult primary sites in addition to the neck may reduce the risk of a subsequent primary above the clavicle. Irradiation of the involved neck only may compromise the use of radiotherapy for a subsequent primary above the clavicle should it become manifest. Surgery for a subsequent primary above the clavicle, when curative radiotherapy cannot be delivered due to previous neck irradiation, may result in the loss of organ function.

The potential occult primary sites to be included in the treatment volume depend on the node location. A single metastatic node in the subdigastric area can arise from a primary in Waldeyer's ring, the hypopharynx or larynx. These potential primary sites, at least on the ipsilateral side, should be included. A single superior, posterior metastatic neck node seldom arises from a primary in the larynx or hypopharynx; they can probably be spared. The nasopharynx is an unlikely occult primary site for a single metastatic node in the mid- or low jugular chain and can probably be spared in this situation. A supraclavicular node usually arises from a primary below the clavicle; treatment with surgery or radiotherapy should be limited to the involved neck when the primary is occult.

When radiotherapy is used, a dose of 50 Gy may be adequate for low risk microscopic disease in the clinically negative neck area. An additional 10–15 Gy boost may be delivered to areas of high risk subclinical disease in the neck following neck dissection or excisional biopsy and to the suspected occult primary sites. A boost dose of 20–30 Gy after 50 Gy to the clinically negative neck area may be necessary to control gross disease in the neck. Electron beam irradiation or oblique fields are used to boost the dose to the gross disease in the posterior neck so that the spinal cord tolerance is not exceeded.

For advanced (stage N2 or N3) operable metastatic neck nodes, a combined approach with neck dissection and pre- or postoperative radiotherapy to the mucosa and neck will provide the optimal local-regional control. For advanced inoperable neck disease, radiotherapy combined with hyperthermia and/or chemotherapy may improve the control rate.

The major drawback of radiotherapy is xerostomia, which can have a significant impact on the patient's quality of life. Impairment of the salivary gland function following head and neck irradiation depends on the volume of the salivary gland included in the irradiation fields and the total dose [28–30]. Franzen et al. [28] showed that following head and neck irradiation with doses ≤ 52 Gy, recovery of secretion can occur beginning 2 months after radiotherapy with a continuous improvement of the salivary flow up to 18 months. With doses >64 Gy, the parotid function became irreversibly depressed in the majority of glands irradiated. With unilateral radiation fields, the majority of

patients experienced no or only slight dryness. With bilateral radiation fields, most patients experienced dryness. The degree of xerostomia was severe and persistent when doses were >64 Gy. Recovery of salivary function may occur even after doses of 50–70 Gy when 50% or more of the salivary gland volume was spared from the radiation beam, although this may not take place until 2–3 years after irradiation [30]. In patients with metastatic neck nodes from unknown primary, since the majority of treatment failures occur in the ipsilateral neck and/or mucosa, routine irradiation of bilateral neck and mucosa to a dose >50–60 Gy is probably not warranted. With 3-dimensional CT treatment planning, it is now possible to minimize the dose to the contralateral salivary glands and reduce the severity of postirradiation xerostomia.

In conclusion, treatment of metastatic neck nodes from unknown primary should be individualized. Proper treatment selection and delivery are essential in achieving optimal cure and quality of life.

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Controversies in the Management of the Lymphatics in Breast Cancer

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Central to the discussion of the management of the lymphatics in early breast cancer is the controversy over whether local control affects survival. An answer to this question is linked to the perception of the natural history of the disease: if the disease is systemic, as maintained by Fisher [1] and others, nodal involvement is seen as an indicator of systemic disease. Local treatment, therefore, is not thought to affect survival. If the disease spreads sequentially, as is the more traditional view, then some disease is considered localized and nodal involvement an instigator of disease spread. In this view, treatment of the lymphatics is necessary because the underlying assumption is that untreated disease will spread [2]. The difference in these two views points to the controversy of whether local control of lymph node involvement in early breast cancer is beneficial to survival.

Examination of the clinical and pathological features of breast cancer suggests that both views are accurate, that is, disease in some patients is localized at the time of diagnosis, while in others it is systemic. Studies and clinical experience show that tumor size and number of positive lymph nodes are good clinical features predictive of the probability of disease spread [3, 4]. In general, smaller lesions and fewer number of positive lymph nodes indicate a greater chance of localized disease, and larger tumors and increased number of positive lymph nodes indicate a greater propensity for spread. However, the fact that not all patients with large tumors or positive lymph nodes have systemic spread of disease, and that some smaller tumors with negative nodes become systemic early, suggest that other less understood prognostic features –

[1] I wish to thank Mary Beth Nierengarten for her editorial assistance.

such as ploidy, S-phase, estrogen/progesterone receptors, and other factors – influence the natural history of the disease. Given what is known about the prognostic features of the disease, why does controversy persist over whether some disease is localized whereby local control can benefit survival?

Why the Controversy?

Several factors over the past couple of decades converged to cast a shadow on the perception that some early disease is localized [5]. Among these factors were studies showing that adjuvant irradiation does not affect, and may be deleterious to, survival [6–8], and other studies showing the benefit of adjuvant chemotherapy on survival in node-positive women [9, 10]. The fact that the survival benefit of adjuvant irradiation continues to be controversial, despite its proven benefit on local control, remains a major argument against the need to treat locoregional disease and has fostered the acceptance of adjuvant chemotherapy as standard treatment for node-positive patients. The 1985 consensus decision of the National Cancer Institute (NCI) for postoperative chemotherapy as standard treatment for premenopausal node-positive breast cancer patients further reinforced the systemic view of the disease [11].

Proponents of the benefits of local control continue to challenge the view that early breast cancer is always systemic and that locoregional adjuvant treatment does not benefit survival. Analyses of the studies that influenced the NCI consensus decision on the benefits of chemotherapy, as well as analyses of the radiation studies that showed the lack of benefit on survival, have shown flaws in trial design and statistical analysis [5, 12, 13]. Inadequate diagnosis and subsequent treatment of local disease, especially of the axillary and internal mammary chain nodes, were major problems in many of the earlier studies on adjuvant locoregional therapies. The proportional increase in recurrence-free survival with the increased number of axillary nodes examined shows the importance of adequate axillary diagnosis (fig. 1) [14]. Similarly, long-term relapse-free survival in many node-positive patients achieved with adequate locoregional therapy shows the importance of appropriate treatment. A 10-year follow-up of 252 stage III breast cancer patients treated by mastectomy, axillary dissection, and radiotherapy at M.D. Anderson Hospital between 1955 and 1984 showed that the number of positive nodes was a strong but not absolute predictor of locoregional control and survival: locoregional control was greater than 95% for 0–3 nodes and 75% for $\geq$4 nodes, and disease-specific relapse-free survival was 63, 48, and 30% for 0, 1–3, and $\geq$4 nodes, respectively [15].

Axillary lymph node involvement also indicates a 25–40% rate of internal mammary chain involvement [2]. Therefore, adequate axillary nodal diagnosis

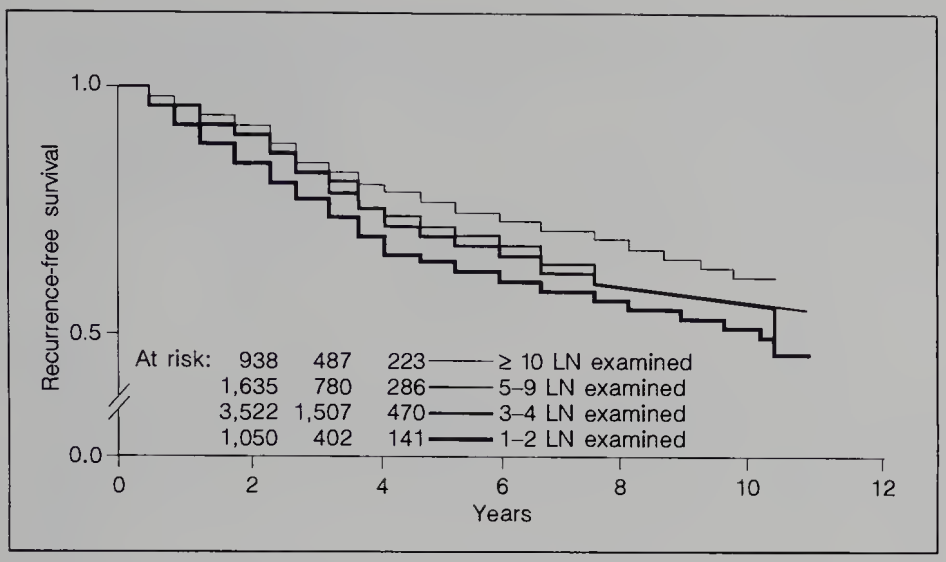

Fig. 1. Low risk patients in the Danish Breast Cancer Cooperative Group 1977 and 1982 Programs (n = 7,145). Median observation time = 76 months. Difference between groups ≥ 10 lymph nodes (LN) vs. <10 LN, p = 0.0001. From [14].

is also important in helping to provide early diagnosis of internal mammary chain involvement. Since the internal mammary nodes are deep under the ribs and sternum and often remain nonpalpable until they reach metastatic size, clinical diagnosis and treatment often are inadequate. Evidence of this can be seen in discrepant reports from studies of local treatment to this area. A study by Veronesi and Valagussa [16] reporting on patients treated by radical mastectomy (RM) versus extended radical mastectomy (including internal mammary chain) (EM) showed a low rate (4%) of clinically detected internal mammary node metastases in patients treated by RM versus a high rate (20%) of pathologically detected nodes in patients treated by EM, but no difference in survival between the two groups. The authors concluded from these results that local treatment did not confer a survival advantage. The unexpected difference in metastases found when the internal mammary nodes were resected, however, may be more indicative of the difficulty of clinically detecting nodal involvement in this area than an indication that treatment of this area does not influence survival. Indeed, the update of the Gustave Roussy study comparing EM versus RM did show a significant decrease in the risk of death (p = 0.05) for node-positive patients with medial tumors treated by EM [17]. This study also reported perplexing results, however, showing that in patients with lateral tumors with positive or negative axillary nodes, EM increased the relative risk of death (RR = 3.07) compared to patients treated by RM (RR = 1). These results remain to be explained.

Table 1. Local failure and treatment sequence [from 18]

Sequence	Percent 4-year crude failure rates (number of failures/total)	Fisher p*	Percent actuarial 5-year failure rates (number of patients observed at 5 years)
RT-FIRST	3 (3/99)	0.03	4 (51)
SAND[1]	2 (1/54)	0.04	8 (32)
CONC[2]	4 (5/116)	0.06	6 (87)
CT-FIRST	15 (4/26)	–	41 (4)

* p values determined as CT-FIRST vs. each other group; other comparisons were not significant; for all four groups not being the same, $p = 0.065$.

[1] SAND = Sandwich therapy: chemotherapy followed by radiotherapy followed by chemotherapy.

[2] CONC = Concurrent chemotherapy and radiotherapy.

Studies on radiation trials have also shown problems with inadequate diagnosis and treatment. As previously mentioned, many of the trials used in the Cuzick meta-analysis, which showed a detriment to survival with irradiation, were found to be flawed [5]. Many of these trials used inadequate radiation techniques. Recht et al. [18] showed that delay in radiation treatment after surgery significantly reduced actuarial local control rates (table 1). Analysis of the first Stockholm trial, showing a survival benefit only to patients treated by surgery plus preoperative radiotherapy as opposed to surgery alone or with postoperative radiotherapy, found that the radiation dose to the internal mammary chain was not adequate in the postoperative group, thereby possibly accounting for the difference in survival benefit between the two radiation groups [19]. An increased number of cardiac deaths in patients in this study, as well as in the study from Oslo [20], indicate another reason for the lack of survival benefit caused by inadequate radiation technique [21].

More recent studies on adjuvant irradiation have shown improvement in survival with the use of adequate radiation techniques, confirming that inadequate irradiation, particularly to the internal mammary chain, used in these earlier studies may account for the lack of demonstrated survival benefit [22–26].

Local Control and Survival: What Do More Recent Studies Show?

Adjuvant Locoregional Therapy

Several studies show the benefit in survival with adequate treatment of the internal mammary chain with either surgery or irradiation. A multivariate

Table 2. Postoperative radiotherapy after radical mastectomy in patients with positive axillary lymph nodes [from 44]

	All patients			Patients with tumors in inner quadrants	
	patients n	local recurrences %	survival at 10 years %	patients n	survival at 10 years %
Villejuif					
Surgery	73	39	42	36	39
		$p<0.01$	NS		$p<0.05$
Surgery + RT	87	14	56	35	72
Stockholm					
Surgery	321	32.4	62	35	60
			NS		
Surgery + RT	639	8.2	68	45	72
Oslo (T_2 tumors)					
Surgery	91	32	52	34	42
		$p<0.01$	NS		
Surgery + RT	95	10	60	38	58

NS = Not significant.

analysis from the Gustave Roussy in Villejuif of node-positive patients treated by mastectomy and complete axillary dissection with either adjuvant complete internal mammary chain dissection or postoperative irradiation to the internal mammary chain showed a decrease in death at 10 years – especially for patients with inner quadrant tumors – compared with patients who received no adjuvant therapy [25, 26]. There was no difference in benefit between the two adjuvant therapies. However, locoregional recurrences, regardless of the tumor site and surgical management of the lymph nodes, were significantly decreased only in the patients receiving adjuvant irradiation. Similarly, node-positive patients, particularly those with inner quadrant tumors, treated with adjuvant irradiation have shown clinically improved survival rates compared to those treated by radical mastectomy alone in both the Stockholm and Oslo studies (table 2) [20, 22, 27].

A recent meta-analysis combining these last two trials assessed the role of adjuvant megavoltage radiotherapy on survival and distant metastases [28]. Patients in both trials were treated by mastectomy and axillary dissection and randomized either into adjuvant postoperative megavoltage irradiation of the regional lymph nodes, including the internal mammary chain, or no postoperative irradiation. Neither trial used chemotherapy. The authors found a signifi-

cant 37% relative reduction of distant metastases in the node-positive patients treated by adjuvant irradiation ($p<0.01$) and a 22% relative reduction of deaths of borderline significance ($p = 0.06$).

Although this meta-analysis does show a statistically significant finding for a relative reduction of distant metastases with irradiation, the borderline significance in relative reduction of deaths points to the problem of power, which is too small in most of the radiation trials to generate statistical significance. As reported elsewhere, it would take 995 patients in the Stockholm trial and 605 patients in the Oslo trial to achieve a p value of 0.05 with a power of 0.8 [5]. The need to increase power and sample size remains problematic. Studies now underway, including a meta-analysis of the more recent radiation trials, will help establish more accurately whether the already noted clinical improvement in survival with adjuvant irradiation can be statistically verified.

Long-term studies suggest that survival rates can be expected to increase, both clinically and statistically, with the use of adjuvant irradiation. Studies from the M.D. Anderson Hospital continue to show that 15-year survival rate curves level out between patients treated by adjuvant radiotherapy alone and the general population [23]. Additionally, a recent study of 328 node-positive patients from the Radiumhemmet, Karolinska Hospital in Sweden showed 15-year contralateral breast cancer rates of 1.8 and 6.7%, respectively ($p = 0.02$), in patients randomized between postoperative radiation therapy versus radical mastectomy alone [29].

Another way to evaluate whether local control affects survival is to look at the differences in survival rates between patients who recur and those who do not. A recent article by Stotter et al. [30] demonstrates the benefit on survival if local recurrence is prevented. Using a mathematical model to predict 5-year survival rates of 499 unilateral breast cancer patients, 49 of whom recurred locally, an 8% deficit in survival was predicted for patients after initial treatment versus a 22% deficit after local recurrence. These predictions were consistent with the actuarial survival rates (fig. 2, 3). Clinical demonstration of the effect of recurrence on survival was shown in a study of 202 patients with invasive breast cancer (size of primary tumor <2 cm, without lymph node involvement) treated with surgery and irradiation. Overall 5-year survival rates and the probability of remaining metastasis-free significantly decreased in patients who relapsed compared with those who did not (fig. 4) [31].

Assessing the benefit in survival by preventing local recurrence is important when critiquing systemic treatments of breast cancer, since studies on adjuvant chemotherapy have shown that patients with 4 or more positive nodes or primaries ≥ 5 cm have not benefitted in terms of local control from chemotherapy alone [32–35].

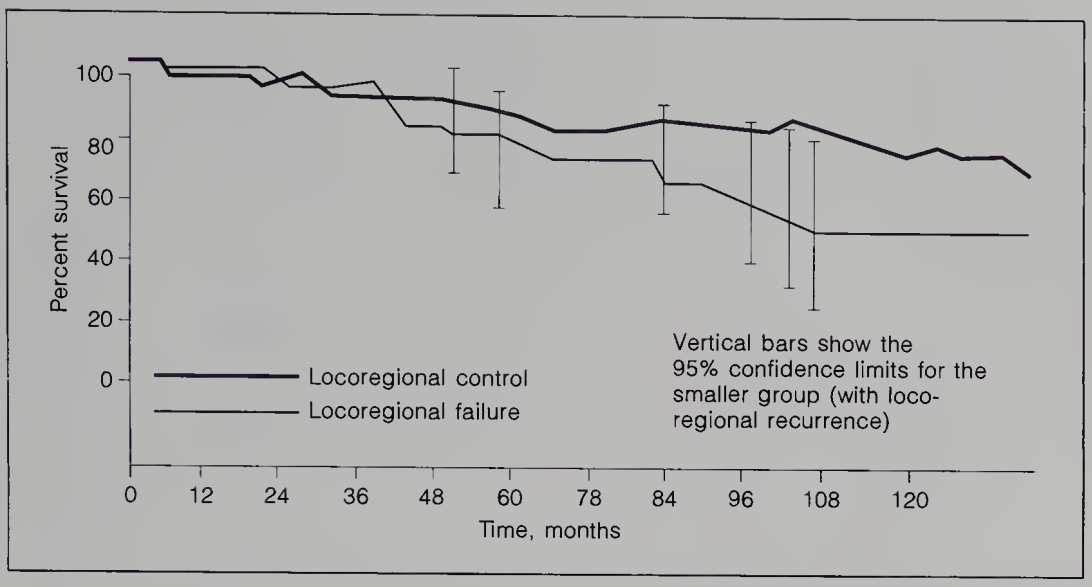

Fig. 2. Comparison of actuarial survival rates of patients whose breast cancer did and did not recur locoregionally [from 30].

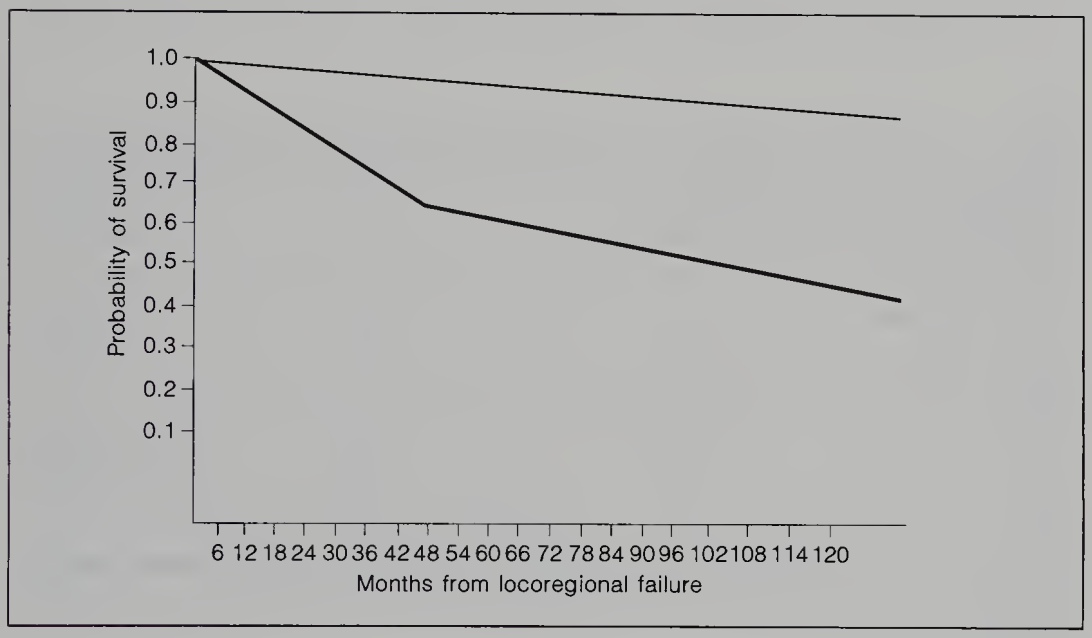

Fig. 3. Predicted survival from the date of locoregional failure (lower curve). The comparison is to predictions for the same patients as if they had not developed locoregional recurrence (upper curve) [from 30].

Adjuvant Systemic Treatment

Systemic treatments, both chemotherapy (for all ages) and hormonal manipulation (for women <50), have been shown to increase recurrence-free survival and decrease local and distant metastases in many patients [36].

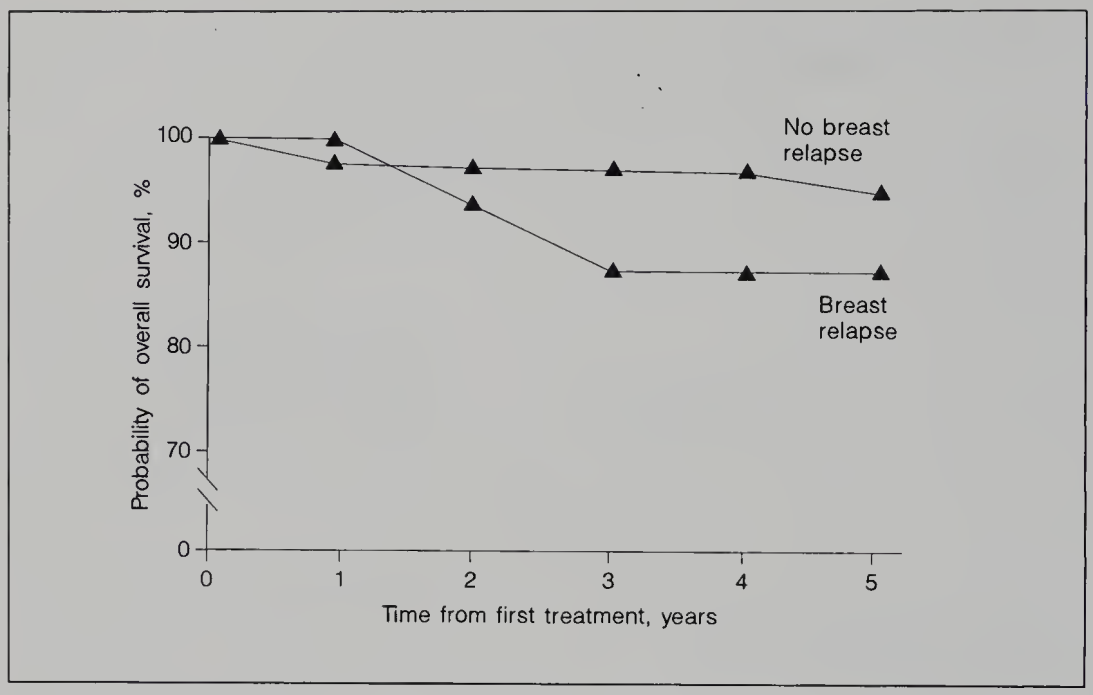

Fig. 4. Influence of local relapse on overall survival (χ^2n = 19.49, p<0.001) [from 31].

However, in patients with 4 or more positive nodes, local control is not significantly improved by chemotherapy alone. (Studies on hormonal manipulation have not broken down local control rates according to the number of lymph nodes involved, but the increased recurrence-free survival in patients treated by hormonal manipulation indicates some effect on local disease [36].) Patients with 1–3 positive nodes treated by chemotherapy alone can expect a 10% locoregional recurrence rate, while patients with >4 positive nodes or with primary tumors ≥5 cm can expect a 20–30% locoregional recurrence rate (table 3) [32–35]. Fowble et al. [35] have noted that since patients with 4 or more positive axillary nodes comprise 30–50% of axillary node-positive patients entered into adjuvant chemotherapy trials, a significant proportion of patients who receive only adjuvant chemotherapy are at risk of developing a locoregional recurrence.

These studies suggest that women with 4 or more positive axillary lymph nodes or primary tumors ≥5 cm should be considered for adjuvant irradiation, since the addition of adjuvant irradiation to chemotherapy has been shown to significantly improve local control in patients with these prognostic factors. A study by the Danish Breast Cancer Cooperative Group showed a statistically significant increase in both local control and disease-free survival, as well as improved overall survival, in patients treated with combined radiotherapy and chemotherapy or radiotherapy and tamoxifen versus either systemic treatment

Table 3. Incidence of locoregional recurrence in node-positive patients receiving post-mastectomy adjuvant chemotherapy [from 45]

Reference	Chemotherapy	Locoregional recurrences, %				Follow-up, years
		all pts	1–3	>4	T_3 tumors	
Stefanik [34] (1985)	CMF	19	9	36	27	5
Fowble [35] (1988)	CMF (PT)	11	7	15	19	3
Griem [32] (1987)	CMF/MF	14	5	–	–	4.4 (median)
	CA	–	–	20	–	
Sykes [33] (1989)	AC	–	10	10	28	2.9

C = Cyclophosphamide; M = methotrexate; F = 5-fluorouracil; P = prednisone; T = tamoxifen; A = adriamycin.

Table 4. Results of systemic treatment alone or combined with radiotherapy at 5 years in high risk patients: Danish Breast Cancer Cooperative Group [37]

Treatment	Local control, %	Disease-free survival, %	Overall survival, %
CMF	72	47	63
CMF + RT	91	54	68
	($p<0.0001$)	($p = 0.002$)	($p = 0.028$)
Tamoxifen	64	38	61
Tamoxifen + RT	94	52	62
	($p = 0.0001$)	($p = 0.0004$)	($p = 0.742$)

C = Cyclophosphamide; M = methotrexate; F = 5-fluorouracil.

alone (table 4) [37]. The efficacy of combining these adjuvant therapies was demonstrated in a study by the Joint Center for Radiation Therapy (table 1) [18].

The inability of chemotherapy alone to benefit local control in some patients emphasizes the importance of assessing the benefit of local control in terms of the different survival rates between patients who recur locally and those who do not.

Table 5. Absolute reduction in 10-year mortality produced by a persistent reduction of 30% or of 15% in the annual odds of death [from 36]

10-year risk of death from breast cancer	Examples of patients at risk	Approximate absolute benefit in annual odds of death of [1]	
		30%	15%
10–20%	stage I, good prognosis	4	2
20–40%	stage I, poor prognosis	8	4
40–80%	stage II, any prognosis	12	6

[1] Difference in numbers alive several years later if 100 women have a persistent reduction in annual odds of death of these percentages.

Optimal Treatment

Studies suggest that local control is most important for patients with small tumors, because treatment of small tumors is predictive of increased survival rates [38, 39]. Other studies show that local control is also beneficial in patients with large tumors. The increase of local recurrence in patients with large primary tumors [40], coupled with evidence that shows a decreased survival rate after local recurrence [30], indicates a need to treat large tumors as well for local control.

These studies and clinical experience suggest that patients with 4 or more positive nodes benefit both in local control and survival from the addition of adjuvant irradiation to postoperative systemic treatment, primarily chemotherapy. Treatment to appropriate areas with adequate doses, while minimizing irradiation of critical normal tissues such as the heart, is essential to achieve optimal results. As mentioned earlier, much of the failure of earlier randomized trials to show survival benefit of adjuvant irradiation may be attributed to inadequate and inappropriate treatment techniques, especially to the internal mammary chain.

A critical question that is difficult to answer, because of the small number of patients affected, is whether irradiation combined with systemic treatment (hormonal therapy or chemotherapy) to patients with 1–3 positive nodes is beneficial. In view of the small effect on survival of these particular treatments in early breast cancer (table 5) [36], even large randomized clinical trials would have difficulty demonstrating a significant survival improvement when combining radiation with chemotherapy or hormonal therapy, especially in this subgroup of patients. Treating patients with 1–3 positive nodes is essentially a

judgement call. Many prognostic factors other than tumor size and number of positive lymph nodes (factors which are not clearly understood and currently under investigation) will help us determine how to treat these patients. Based on my clinical experience and that of others, I recommend that women with 2 or more positive nodes be treated with adjuvant irradiation to the peripheral lymphatics only. Peripheral lymphatic and chest wall irradiation should be included for patients at high risk for locoregional recurrence (i.e., 4 or more positive nodes, large primary tumor with grave signs, and tumors located in the central or inner quadrant of the breast associated with positive axillary nodes) [41]. Because early breast cancer has a high probability of being localized, determining which patients will benefit from local treatment is critical and is a strong argument for early diagnosis.

Conclusion

How to treat the lymphatics in early breast cancer leads to the larger interrelated questions of the disease itself: the natural history of the disease, the relationship between local control and survival, and the benefits of different adjuvant therapies according to endpoint. A question posed several years ago by Gilbert Fletcher [23] articulates well the practical implications of how we answer these larger questions: 'Asking whether breast cancer is a curable disease has conceptual merit, but the question can lead to therapeutic nihilism: if the disease is not curable, what good does it do to treat it, and particularly to prevent local-regional recurrence?' Similar to the term 'fatalistic' used to define the systemic view of breast cancer [42], the term 'therapeutic nihilism' denotes the gravity in how we perceive and subsequently treat this disease. Efforts to treat this disease more effectively demand that we not become polarized in our views on any of these larger questions, but that we, as Tubiana [43] suggests, view the advances in both local and systemic treatments as complementary, not as contradictory.

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The Role of Surgery in N1 and N2 Lung Cancer

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Prognosis in carcinoma of the lung is influenced by the stage of the disease at presentation and by the treatment that can be rendered. It is now standard practice to carefully stage all carcinomas of the lung, using the international TNM criteria for cancer staging [1]. Briefly stated, tumors confined to lung without any metastases, regional or distant, are classified as stage I, and tumors associated with only hilar or peribronchial lymph node involvement (N1) as stage II. Locally advanced tumors with mediastinal or cervical lymph node metastases, and those with extension to chest wall, mediastinum, diaphragm or carina are classified as stage III tumors. Finally, tumors presenting with distant metastases (M1) are classified as stage IV disease.

Curative treatment requires effective control of the primary tumor before metastases can occur, and in non-small cell lung carcinoma, surgical treatment is still regarded as the most effective method of controlling the primary tumor (provided it is resectable and the risks of the procedure are low). Surgical treatment is generally offered to all patients with stage I or II disease and to specific groups of patients with stage III disease.

Patients with stage I carcinoma of the lung are presumed to have early lung disease, and are most curable by resection with a 5-year survival expectation of 72% [2]. Patients with stage III and IV carcinomas are viewed to have advanced tumors and a poor prognosis, though some of them benefit from surgery or combined modality therapy that includes surgery. There remains a small, intermediate group of patients who present with early invasion into hilar or pulmonary nodes (N1) as the sole site of tumor spread, i.e., stage II patients. The affected nodes in this latter group are referred to as N1 and include four levels of nodes: hilar, interlobar, peribronchial and segmental. Most of these

nodes are contained within the pleural envelope and are generally removed as part of the surgical resection of the primary.

Role of Surgery in N1 Lung Cancer

Because of the relatively small number of patients who have stage II lung cancer, it has been difficult to assess whether they represent variants of early stage disease, or should be viewed as advanced cancers and treated with combined modality therapy. This group of patients benefits from complete surgical resection with mediastinal lymph node dissection. However, more than one-half of them have recurrence in the course of their follow-up. Few have been treated with irradiation or chemotherapy postoperatively, and no single institution has been able to recommend adjuvants to enhance survival in these patients.

From 1973 to 1989, 214 patients were treated by resection at Memorial Sloan-Kettering Cancer Center for stage II non-small cell lung cancer [3]. This represents 9% of all resections performed by us for lung cancer during that period. The median age was 62 years. The histology was adenocarcinoma in 116 and squamous cancer in 98. Bronchoalveolar carcinomas and large cell cancers were grouped under adenocarcinomas.

The extent of resection depended on the location of the tumor. Lobectomy was performed in 68% of the patients, pneumonectomy in 31% and wedge resection or segmentectomy in 1%. Lobectomy was sufficient to encompass all disease in 34 of 35 T1 tumors. Of interest was the fact that regardless of histology, half of the patients treated by resection had a single involved N1 node and 85% had involved nodes in only one N1 level.

After surgery, most patients received no further treatment. Twenty-two percent had postoperative irradiation and only 5% had postoperative chemotherapy.

Survival was calculated by the Kaplan-Meier method. The overall survival following resection was 39%. There was no survival difference between T1 and T2 tumors. There was a difference in survival by tumor size (fig. 1). Patients with tumors 3 cm or less in diameter had a 5-year survival of 47%, compared to those with tumors 5 cm or greater where the 5-year survival was 29%; this was significant with a p value of 0.021. There was a statistically significant difference in survival between patients with involvement of a single N1 node versus multiple N1 nodes (45 vs. 31%) (fig. 2). There was some difference in survival between patients with squamous cancers as opposed to those with adenocarcinomas (44 vs. 34%). There was no difference in survival by location of the tumor, nor by the extent of resection performed.

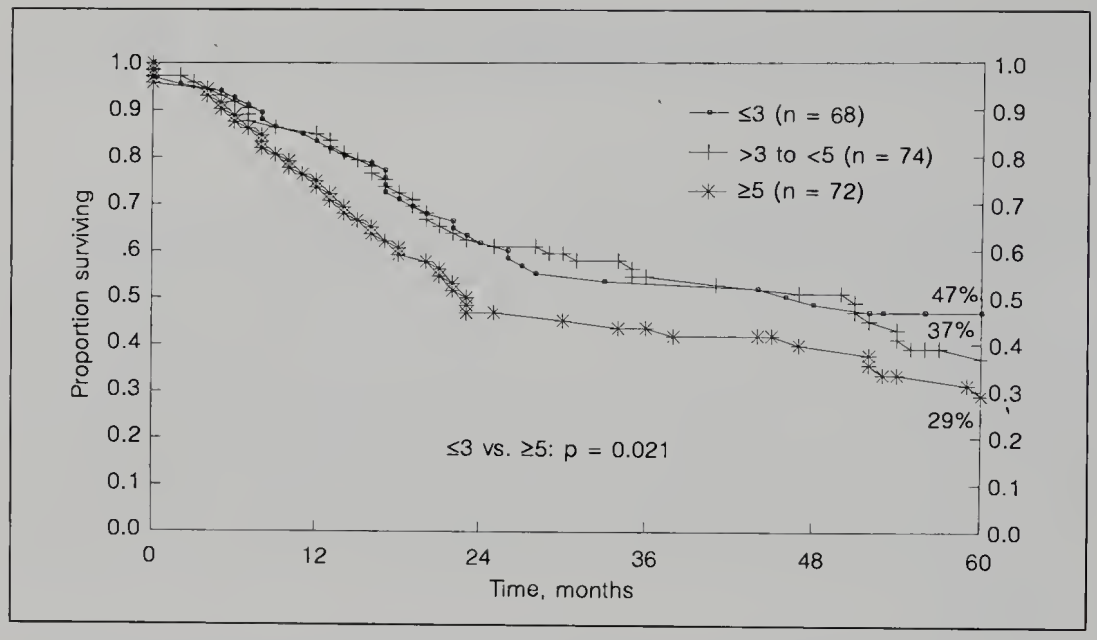

Fig. 1. Survival following resection in stage II lung cancer by tumor size.

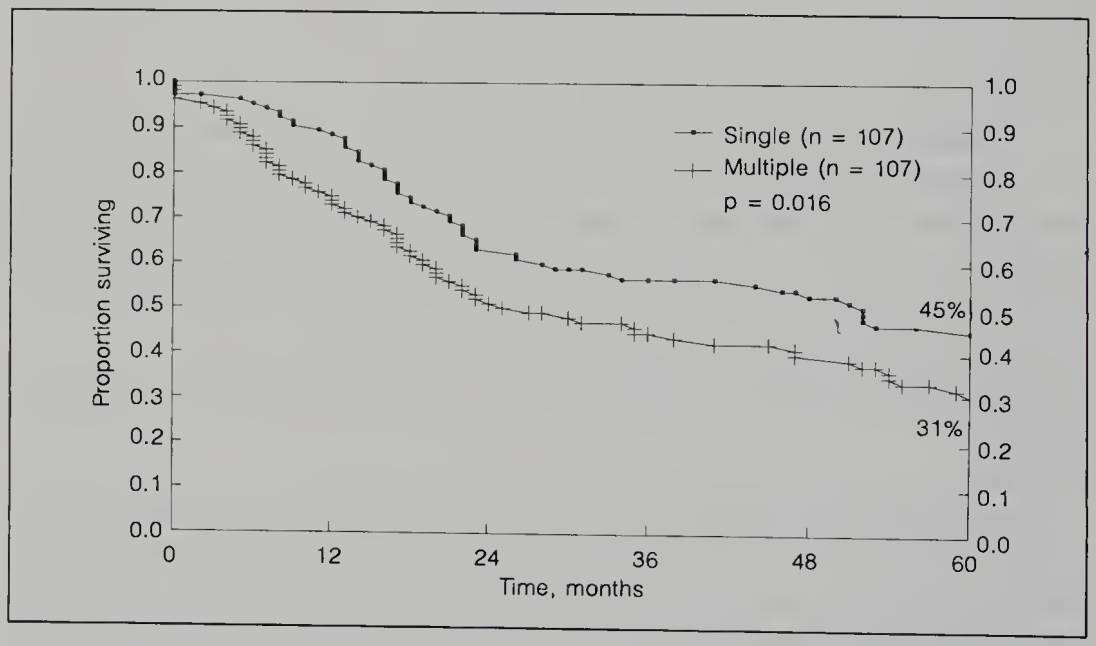

Fig. 2. Survival following resection in stage II lung cancer by number of involved nodes.

The recurrence rates were high despite a complete resection. The patterns of recurrence varied by histology, with more local recurrences in patients with squamous carcinoma. But the most common site of recurrence for all cell types was the brain. The incidence of local recurrence was influenced by radiation

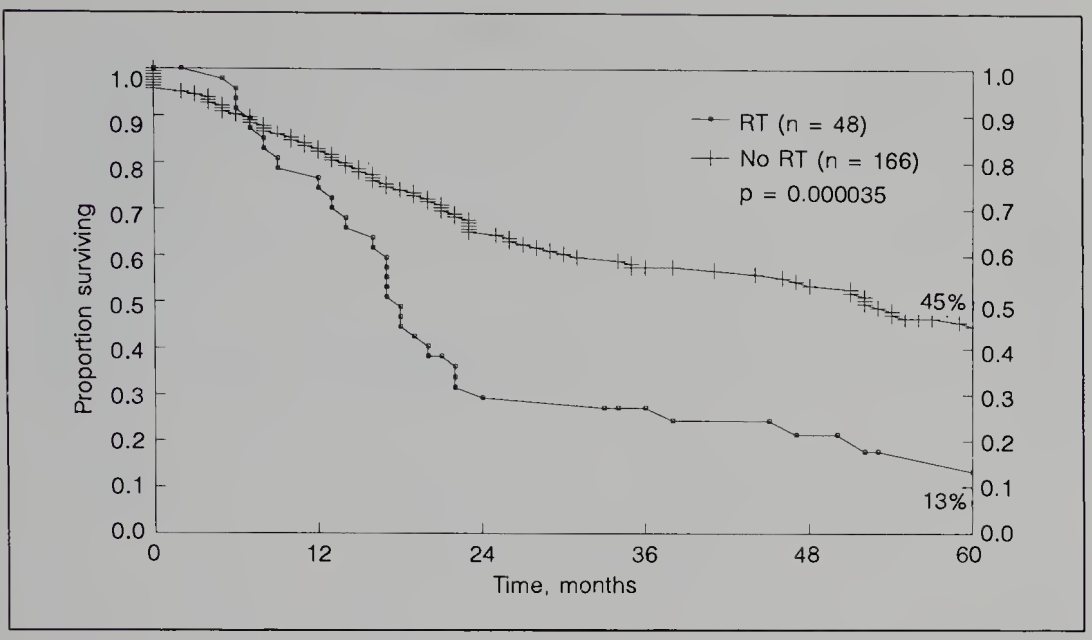

Fig. 3. Survival following resection ± postoperative radiation therapy in stage II lung cancer.

therapy when given: there were fewer local recurrences in patients who received radiation therapy, particularly in those with squamous cancers. This difference was not apparent in patients with adenocarcinoma. As to survival, patients who received postoperative radiation therapy did significantly worse than those who did not (fig. 3). However, the majority of the patients had received no radiation after resection and the decision to give radiation was arbitrary and not standardized. Our interpretation of this was that radiation therapy was given to a worse group of patients, but that radiation did not greatly help. They remained, therefore, the worse group. We concluded that many patients with stage II lung cancer achieve long-term survival with surgery, and the favorable prognostic factors are tumor size and number of involved nodes, and perhaps the histology.

Postoperative external radiation therapy seems to reduce the incidence of local and regional recurrence, at least in squamous carcinoma, without affecting the ultimate survival.

Most recurrences are distant metastases, suggesting the need for effective systemic treatment once nodal involvement is present. The specific regimens that might benefit these patients require further study.

Two large cooperative studies have attempted to address this group of patients. The Lung Cancer Study Group randomized 189 resected stage II patients by histology to receive adjuvant treatments. Those with resected

squamous cancers were treated by postoperative external irradiation or received no further treatment [4]. In resected stage II adenocarcinomas, the randomized arms of the trial were cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy or immunotherapy [5]. These studies concluded that in squamous carcinoma, postoperative radiation therapy reduced local and regional recurrence but had no impact on survival. In adenocarcinoma, chemotherapy had a survival advantage over immunotherapy. The drawbacks of these studies were that stage II and III resected lung cancers were grouped together and no separate analysis of patients with stage II carcinomas was reported. The Lung Cancer Study Group reported a survival difference between patients with squamous carcinoma and adenocarcinoma, and between T1 and T2 lesions.

The second large cooperative trial was conducted by the Ludwig Lung Cancer Study Group from Europe [6]. It evaluated resected stage II carcinomas for survival and recurrence. There were 253 patients with stage II disease entered into the study (81 T1N1 and 172 T2N1). Only median survivals were reported, and these indicated that patients with T1 lesions lived twice as long as patients with T2 disease (median T1 = 4.8 years, T2 = 2.3 years).

Primary Surgery in N2 Lung Cancer

Metastasis to mediastinal lymph nodes (N2 disease) is probably the most common deterrent to cancer cure in spite of a localized presentation. Mediastinal metastasis is noted in nearly half of all patients with non-small cell lung carcinoma. Many view this large group of patients to have incurable disease despite the best efforts of surgery and radiation therapy.

From 1974 to 1981, a total of 1,598 patients with non-small cell lung cancer were seen at our institution; 706 of them had mediastinal lymph node metastases. Of these, 151 were completely resected; their histology was adenocarcinoma in 94, squamous cancer in 46 and large cell carcinoma in 11 [7].

The overall 5-year survival was 30%. There was no difference in survival at 5 years between patients with adenocarcinoma (30%) and those with epidermoid carcinoma (32%) [8]. However, survival was affected by tumor size and number of involved N2 nodes. Better survival at 5 years was noted in patients with small tumors (T1 46%), as compared to large tumors (T2 27%) or those with extension outside lung or proximity to carina (T3 14%) ($p = 0.003$). Also, patients with a single involved N2 node did better than those with multiple nodal involvement at one or more levels ($p = 0.005$) (fig. 4).

We concluded that there is benefit from resection in some patients presenting with carcinoma of the lung and mediastinal nodal involvement since long-term survival of 5 or more years after resection is noted in 30% of the patients.

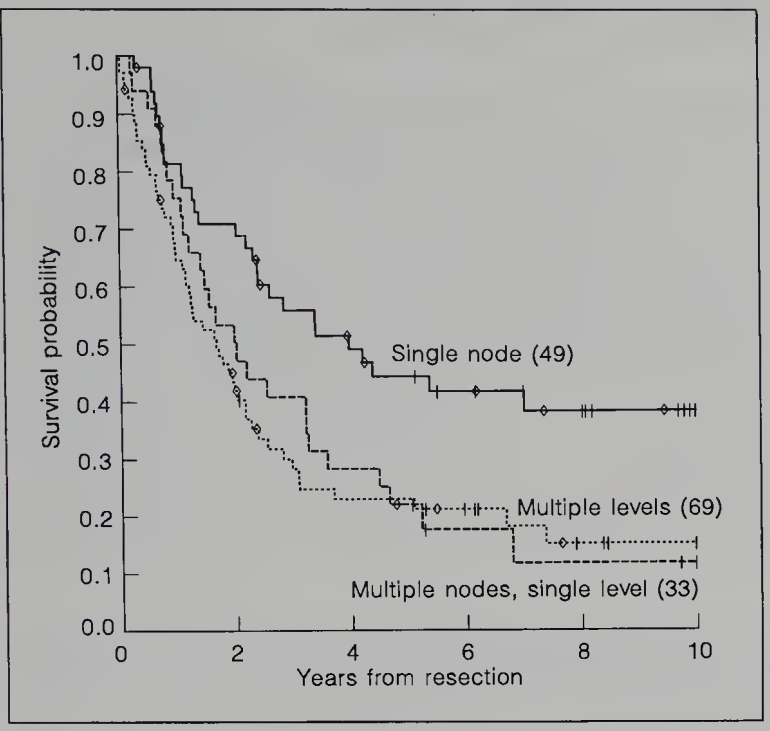

Fig. 4. Survival of patients with resected N2 lung cancer by number and level of involved nodes.

Table 1. Memorial Sloan-Kettering Cancer Center experience, non-small cell lung cancer

Patients suitable for primary surgical treatment are those with:
(1) Peripheral primary tumors (T1 or T2)
(2) Normal mediastinum on chest roentgenograms, bronchoscopy and CT scan, or a single but well-encapsulated ipsilateral lymph node enlargement
Patients who do not benefit from initial surgical treatment are those who present with:
(1) Bulky mediastinal lymph node metastases
(2) Multiple levels of lymph node involvement in the ipsilateral mediastinum or subcarinal space on chest roentgenograms, CT scans or mediastinoscopy

We identified those that best benefited from surgery as their primary treatment to have peripheral tumors (T1 or T2), a normal mediastinum on chest roentgenograms and at bronchoscopy, and a normal mediastinum on computerized tomographic (CT) scan or with a single but well-encapsulated ipsilateral lymph node enlargement (table 1).

We identified the patients who do not benefit from surgical treatment to be those seen with bulky mediastinal lymph node metastases or multiple levels of lymph node involvement in the ipsilateral mediastinum or subcarinal space on chest roentgenograms, CT scans or mediastinoscopy. In an effort to improve survival in this group of patients, we began using chemotherapy preoperatively [9].

The rationale for combining preoperative radiation therapy with chemotherapy in some studies is based on the expectations of additive or synergistic effects. First, we elected to study a relatively homogeneous group of patients seen with bulky N2 disease, since these represent a large segment of the lung cancer population with a uniformly poor prognosis. Second, we chose to use only one mode of preoperative treatment, chemotherapy, to assess its benefit before evaluating the merits of combined preoperative chemotherapy and irradiation.

From 1984 to 1991, we identified 136 patients with non-small cell lung cancer and N2 disease that would not have benefited from primary surgical treatment and offered them preoperative chemotherapy [10]. N2 disease was confirmed histologically in all patients either by mediastinoscopy or at thoracotomy. The median age of the group was 55 years. Only 29% were squamous cell cancers; 71% were adenocarcinomas or large cell cancers; 70% had either T1 or T2 lesions.

The treatment plan was as follows: all patients first received 2–3 cycles of MVP chemotherapy. The MVP regimen consisted of cisplatin (120 mg/m^2), a vinca alkaloid (vindesine 3 mg/m^2 or vinblastine 4–4.5 mg/m^2), and mitomycin 8 mg/m^2. Response to chemotherapy was radiographically assessed and responders went to surgery, where complete resection was carried out whenever possible. Chemotherapy responders received additional chemotherapy postoperatively and those with persistent metastases in lymph nodes also received radiation therapy.

The median time from start of chemotherapy to surgical treatment was 3 months. Major radiographic response was noted in 105 patients (77%). Complete radiographic response (CR) was recorded in 13 patients, and partial response (PR) in 92.

Following chemotherapy, 114 patients were surgically explored and 89 (65% of the original 136) had a complete resection. Sixty percent had a lobectomy, 13% a pneumonectomy and 11% a wedge resection or segmentectomy. Brachytherapy was used in 21 patients who had incomplete or no resection.

Because of tumor regression after chemotherapy, the postsurgical stage of the disease had improved in 39% of the patients explored. Nineteen had no

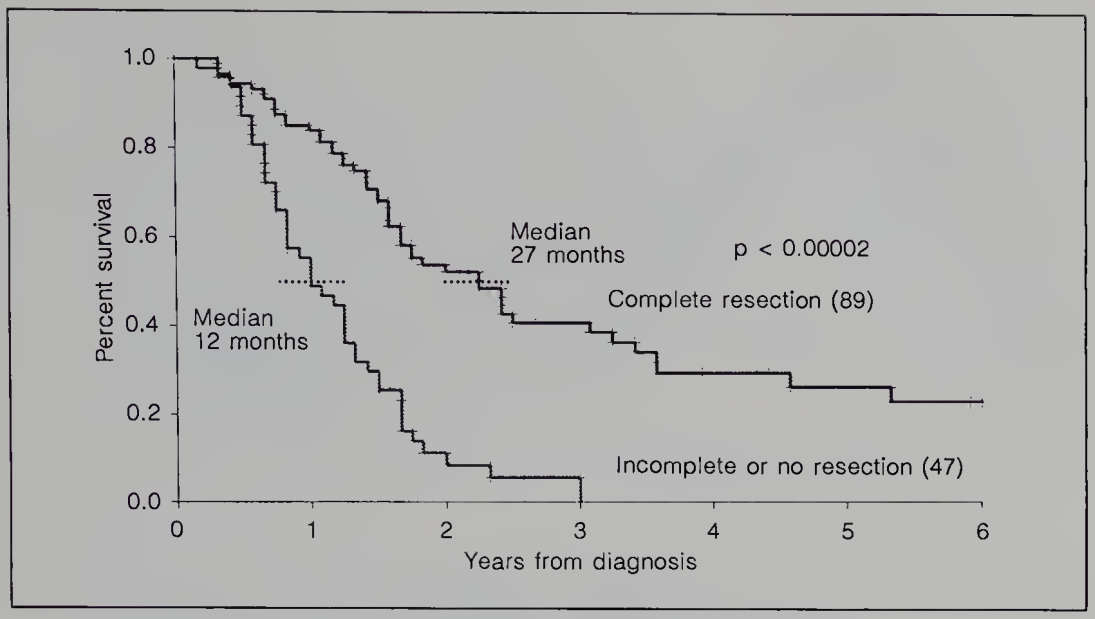

Fig. 5. Survival by extent of resection following chemotherapy.

tumor and an additional 25 had no residual metastasis in N2 nodes. The remainder had persistent disease in lung and nodes.

Relating chemotherapy response to resectability, 93% of major responders to chemotherapy (CR or PR) went to surgery and 86% of these had complete resection of their tumor.

Nearly two-thirds of all the patients treated with preoperative chemotherapy had complete resection and nearly 80% of patients who had major response to chemotherapy had a complete resection. These results are comparable to, if not better than other drug regimens used with or without the addition of preoperative irradiation [11–13].

Survival was calculated from the start of chemotherapy. The overall survival at 3 years was 28% with a median survival of 19 months. There was a significant difference in survival between patients who had complete resection of their residual tumor as opposed to those who had less than that, with a p value of 0.00002 (fig. 5). The median survival following complete resection was 27 months with a 3-year survival of 41%, whereas the median survival with incomplete or no resection was 12 months with a 3-year survival of 5%.

Survival was best in patients who had complete pathologic response to chemotherapy with no residual tumor found at surgery. Their survival was 71% at 3 years with a median survival of 64 months. There was no difference in survival between patients with squamous cell cancers and those with adenocarcinoma or large cell cancers.

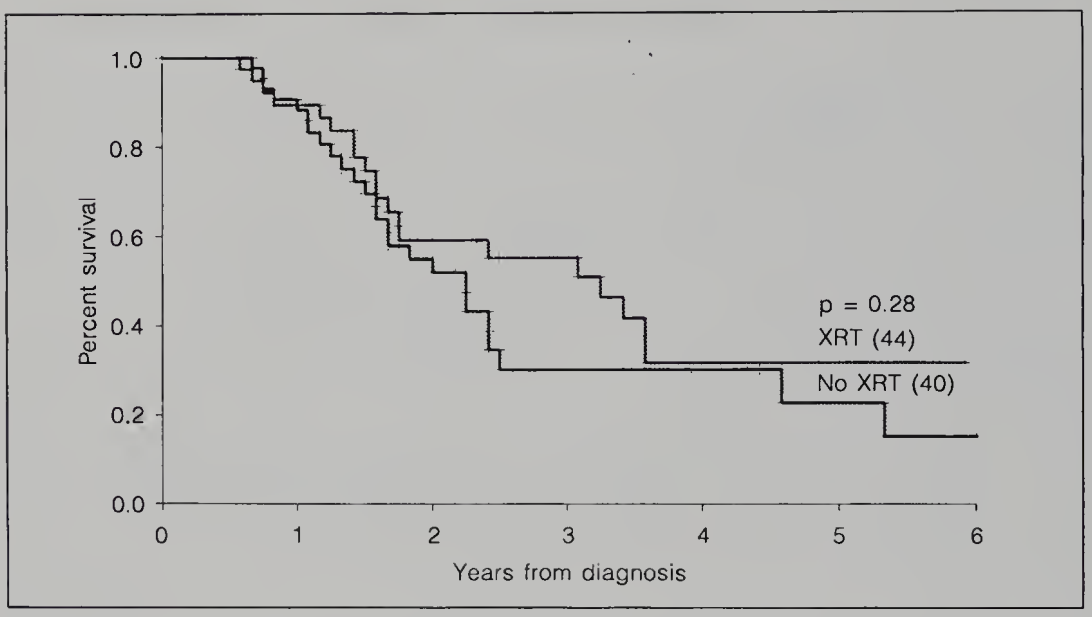

Fig. 6. Survival following chemotherapy and surgery ± postoperative external radiation therapy.

Seventy-eight of the 136 patients (114 explored) received postoperative radiation therapy to the mediastinum. Among those who had complete resection of their tumor, 44 had radiation therapy and 40 did not. The only survivors were patients who had complete resection. Although selection of radiotherapy was not prospectively randomized, there was no evidence that postoperative external radiation therapy provided additional benefit (fig. 6).

To date, 33 patients have had no recurrence of their cancer following treatment; all had a complete resection; 28 of these are alive and well, and 5 have since died of unrelated causes. All pulmonary complications, suspected to be due to mitomycin toxicity, occurred after 3 cycles of chemotherapy and most were reversible with steroid therapy. There were 7 treatment-related deaths in our entire series of 136 patients for an overall treatment-related mortality of 5%. This number includes postoperative as well as chemotherapy deaths.

The results of the current study of 136 patients with clinically demonstrable N2 metastases indicate several important findings. First, available combination chemotherapy with demonstrated activity in patients with more advanced disease can result in major tumor regression in a large percentage of patients with clinical N2 disease. Second, complete resection is feasible and can be accomplished in the majority of responding patients. Third, the ultimate goal is complete sterilization of the tumor. However, complete resection is essential in patients with residual disease if prolonged survival is to be attained.

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Management of Hilar and Mediastinal Lymph Nodes with Radiation Therapy in the Treatment of Lung Cancer

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As in all forms of cancer, treatment of carcinoma of the lung must be based on knowledge of the modes of spread. Along with local spread and distant metastasis, lymphatic spread is one of the three important pathways of progress of bronchogenic carcinoma. Thus, a thorough knowledge of the lymphatics of the lungs is important when patients with lung cancer are treated.

Thoracic Lymph Nodes

Historically, lymph nodes draining the lungs are conveniently divided into two main groups: (1) pulmonary and (2) mediastinal nodes. The pulmonary nodes are divided into intrapulmonary and bronchopulmonary, and the latter are subdivided into interlobar and hilar. The mediastinal nodes can be divided into anterior and posterior mediastinal, tracheobronchial, and paratracheal. These anatomic descriptions have been incorporated into the American Joint Commission (AJC) TNM staging of lung cancer [1, 2].

Lymphatic Drainage of the Lung

The drainage for each pulmonary lobe is shown in figures 1 and 2. Lymph from the right upper lobe flows to the right tracheobronchial lymph nodes. Lymph from the middle and lower left lobes drains into lobar, interlobar, and

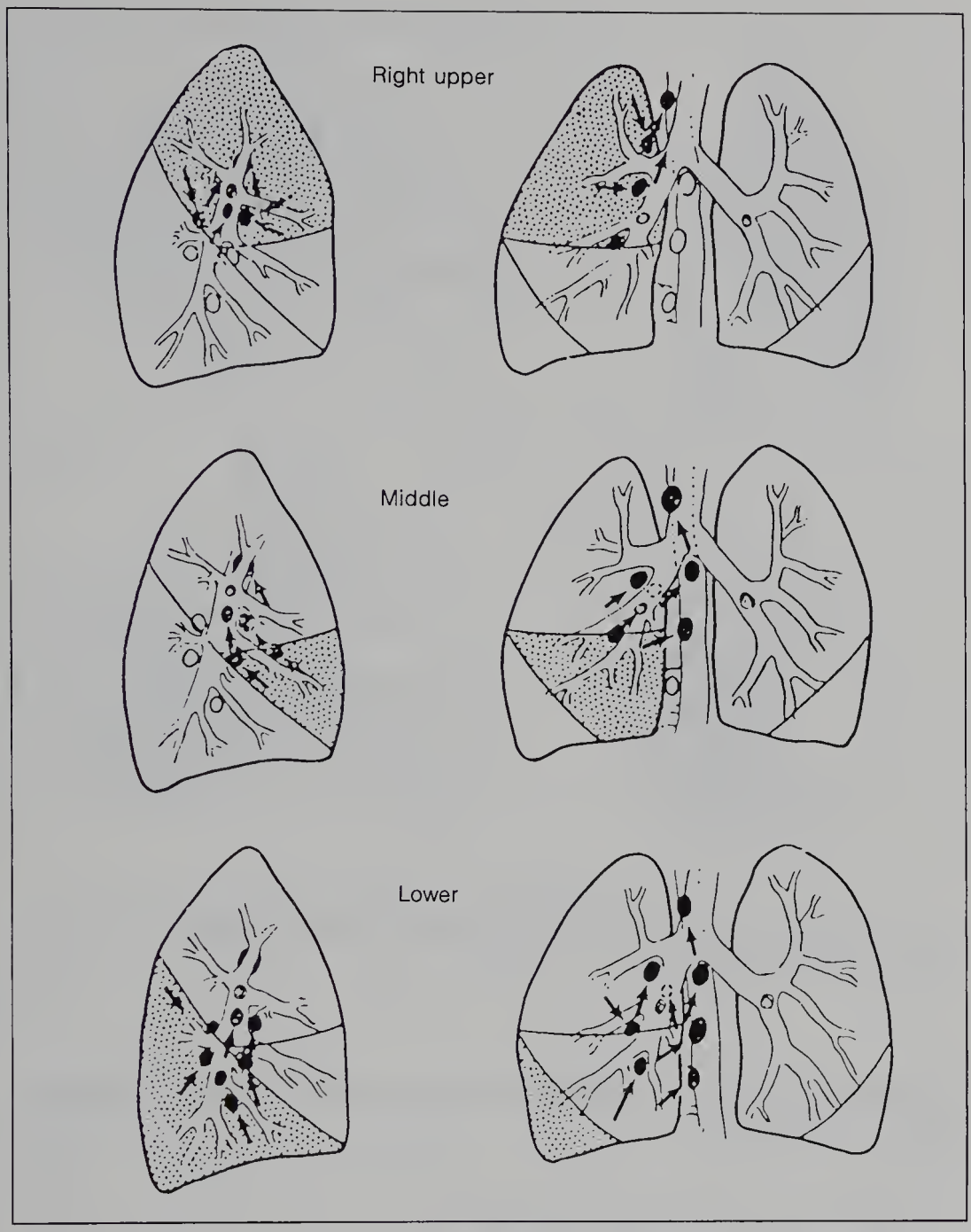

Fig. 1. Diagram illustrating the lymphatic drainage of three lobes of the right lung. Redrawn by permission [10].

finally hilar nodes to the subcarinal and ipsilateral mediastinal nodes. Lymph from the left upper lobe flows not only to the venous angle of the subclavian and internal jugular veins of the same side, but also often crosses over to the right mediastinum. Lymph drainage from both lower lobes can also go to the

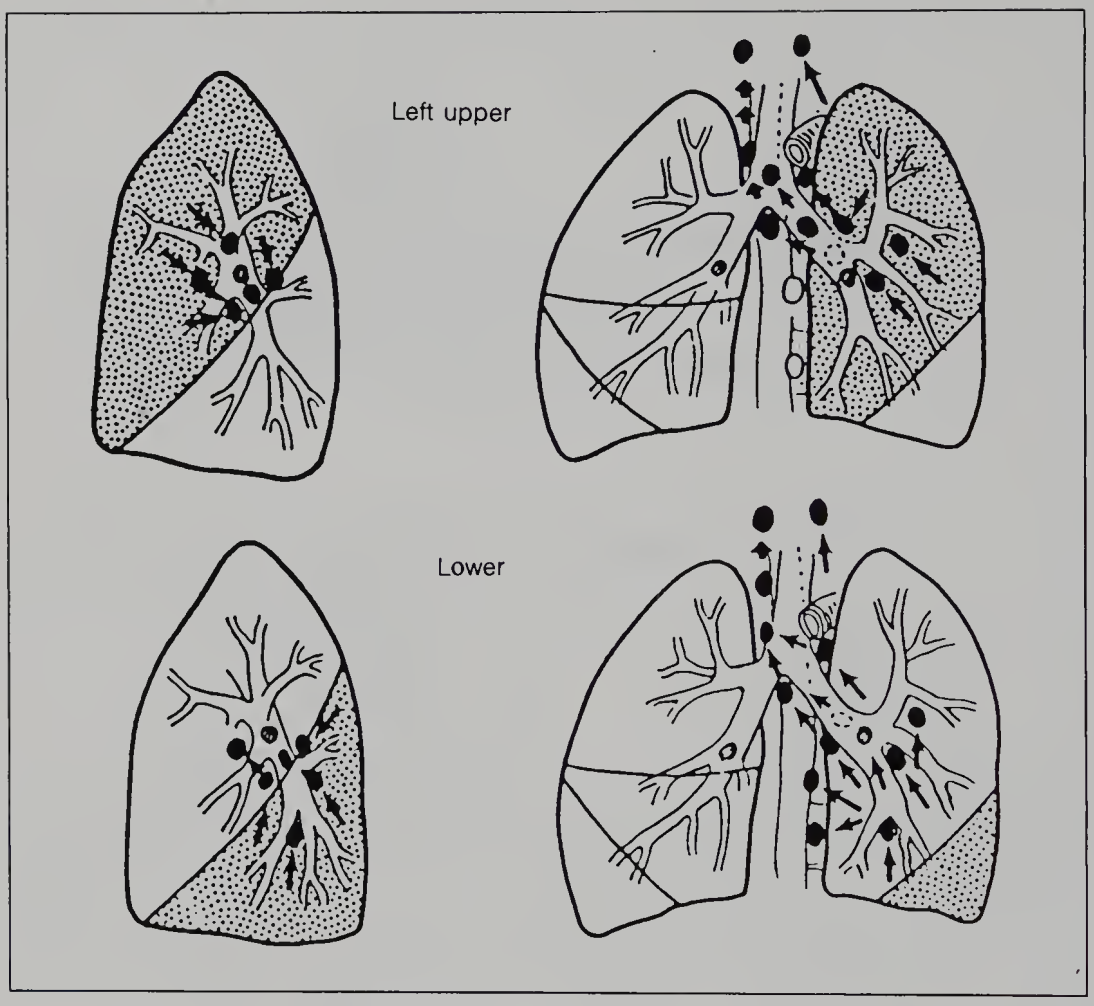

Fig. 2. Diagram illustrating the lymphatic drainage of the two lobes of the left lung. Redrawn by permission [10].

pulmonary ligament and paraesophageal nodes. Invasion of the contralateral hilum is exceedingly rare.

Incidence of Lymphatic Involvement

The incidence of nodal involvement in lung cancer varies in reported series, depending on patient selection, from about 35 to 40% for the lobectomy series to 70–80% for autopsy series (table 1). The incidence of hilar nodal metastasis from lung cancer is approximately 60% for the upper lobes and about 75% for the lower lobes [3]. The incidence of mediastinal adenopathy is 40–50% of operative specimens [4]. Scalene node involvement ranges from 2 to

Table 1. Incidence of lymph node involvement in lung cancer

Study (first author)	Cases	%
Lipshitz [34]	200 resected	40
Watanabe [35]	540 resected	38
Bourgeon [36]	295 resected	37
Line [37]	681 autopsies	70

Table 2. Lymph node metastasis in operative specimens [modified from 5]

Primary site	No node metastases %	Hilar node metastases %	Mediastinal node metastases %	Supraclavicular	
				right %	left %
Right upper lobe and right hilum	40.5	59.5	40.5	30	0
Right middle lobe	36	64	19	30	0
Right lower lobe	23	77	54	3	0
Left upper lobe and left hilum	27	73	46	9	31
Left lower lobe	24	76	40	8	0

Table 3. Mediastinoscopy series (n = 179) [from 4]

Primary site	Patients, n	Positive nodes, n (%)			
		total	ipsi-lateral	contra-lateral	bilateral
Right lung	108	57 (53)	22 (38)	1 (2)	34 (60)
Left lung	71	29 (40)	13 (45)	7 (24)	4 (31)
Total	179	86 (45)	35 (41)	8 (9)	43 (50)

37%. Metastasis to the scalene nodes is primarily from ipsilateral upper and right middle lobe tumors (table 2) [5]. Incidence of nodal metastasis according to site of the primary tumor is shown in tables 2 and 3, and according to histology in table 4.

Table 4. Overall incidence of hilar and mediastinal nodal metastasis (all male except 4) [modified from 38]

Histology	Nodal metastasis n (%)
Squamous cell carcinoma	95/126 (77)
Oat cell carcinoma	96/102 (96)
Adenocarcinoma	88/100 (80)
Large cell undifferentiated	67/80 (84)
Total	346/418 (83)

Pretreatment Assessment of Regional Node Metastasis in Lung Cancer

During the last two decades, voluminous literature has demonstrated the relative usefulness of radiologic studies such as computed tomography (CT) and magnetic resonance imaging (MRI) in the pretreatment assessment of metastases in thoracic lymph nodes [6, 7]: despite the advances in nonsurgical staging, there is still a high percentage of false-negative and false-positive findings resulting in low specificity and low sensitivity. It is generally accepted that mediastinoscopy (limited thoracotomy if the primary is in the left side) is the only true means of assessing the metastatic status of mediastinal lymph nodes [8].

Staging

Current AJC definitions for lymph node metastasis of lung cancer are as follows [1]: Nx = regional lymph nodes cannot be assessed; NO = no regional node metastasis; N1 = metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes, including direct extension; N2 = metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s); N3 = metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s).

The curent AJC staging system for lung cancer is shown in table 5. This illustrates the importance of nodal metastasis in staging: patients with primary T1–T2 tumors and *NO* are assigned to stage I, T1–T2 tumors and *N1* to stage II, and T1–T2 tumors and *N2* to stage III. Analysis of recent surgical series that have reported an improved 5-year survival in patients with ipsilateral mediastinal disease has resulted in a modification of the AJC staging system. In their

Table 5. AJC staging system for lung cancer [from 1]

Occult	Tx	N0	M0
Stage 0	Tix	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N2	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	any T	N3	M0
	T4	any N	M0
Stage IV	any T	any N	M1

new staging system [2, 3] shown above, ipsilateral mediastinal nodes are designated as N2, and contralateral node involvement has been grouped with supraclavicular nodal disease as N3. Similarly, former stage III has been divided into stage IIIA (ipsilateral mediastinal node metastasis) and stage IIIB (contralateral mediastinal as well as supraclavicular nodal disease).

Although the earlier staging system had significant therapeutic implications as well as prognostic value, it also showed deficiencies in the anatomic descriptions of regional lymph nodes in lung cancer. Commonly accepted, specific anatomic definitions of each nodal station were lacking. For example, the nodal stations referred to as mediastinal or superior mediastinal did not permit localization of the specific anatomic site within the mediastinum. Moreover, such designations did not lend themselves to a comparison of patient data from different series. In 1981, a task force from the American Thoracic Society (ATS) was formed to address some of these issues. As a result of their work [9], the thoracic nodes were divided into 13 different stations (fig. 3), now the basis of the recent AJC staging system [1]. The major advance in the ATS report was that clinically identifiable anatomic structures were the basis of the map, and specific anatomic limits were prescribed for each nodal station. The compatibility of the AJC and ATS nodal classifications is shown in table 6 [9]. The highlights of this new classification were that the boundaries of the critical lower paratracheal nodal station were defined and the designation of 'hilar' dropped because of the ambiguity of the radiologic use of this term. The

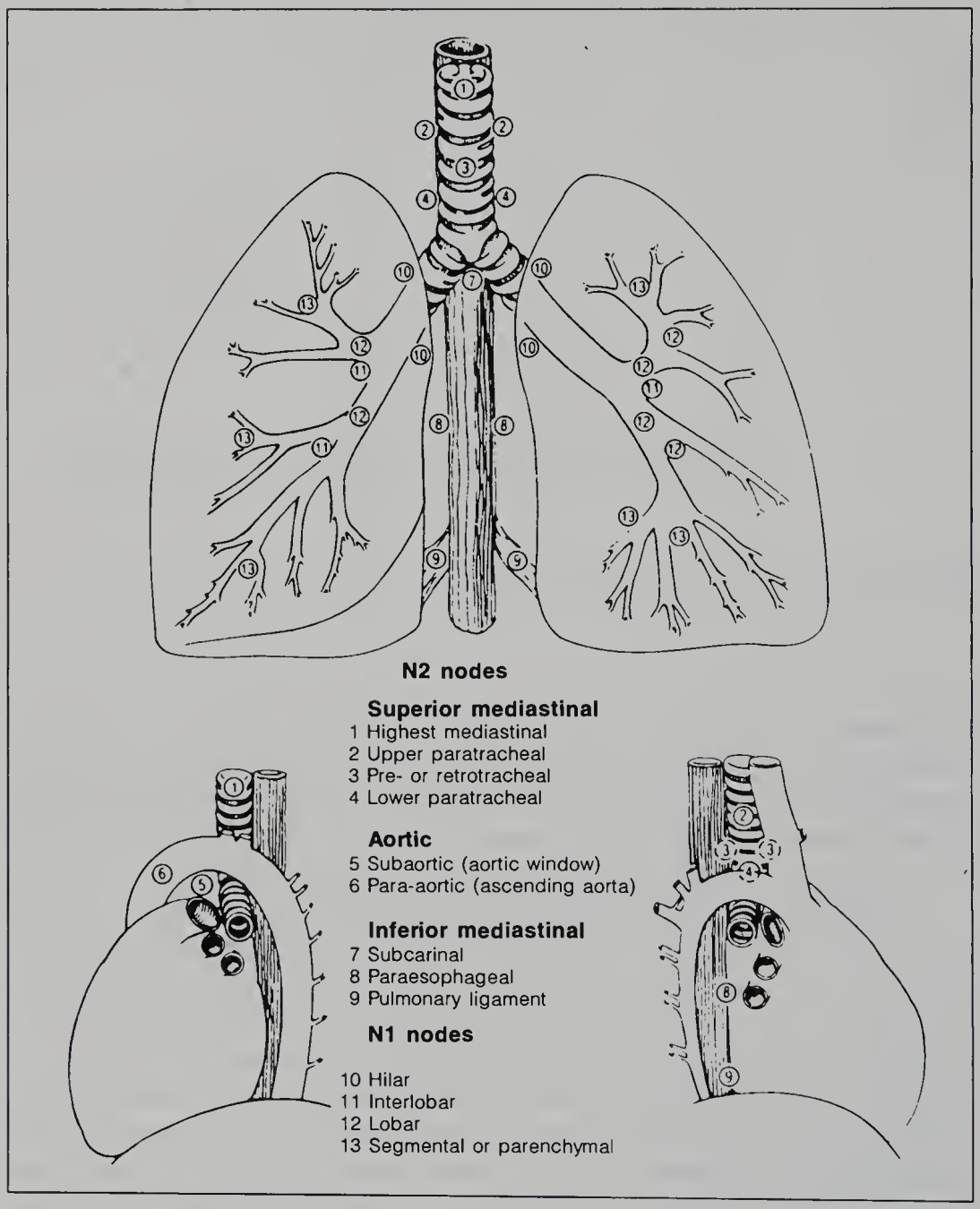

Fig. 3. Sites of lymph nodes [from 27].

first intrapulmonary nodal station would be nodal station 10. Despite apparent significant improvement in the definition of various nodal stations and acceptance of this mapping system by most thoracic surgeons, it is not yet widely accepted and used by other specialties dealing with lung cancer (i.e. radiation oncology).

Table 6. Compatibility of AJC and ATS classifications [from 9]

Nodal station	AJC	ATS
1	Highest mediastinal	Included in station 2
2	Upper paratracheal	Essentially unchanged
3	Pre- and retrotracheal	If pretracheal, included in regions 2, 4, or 6 depending on anatomic location; if retrotracheal, included in region 8
4	Lower paratracheal	Boundaries for this *critical* station are defined
5	Subaortic	Renamed aortopulmonary to include nodes along the lateral surfaces of the aorta and left or main pulmonary artery as well as those along the aortopulmonary window
6	Para-aortic	Renamed anterior mediastinal nodes; includes some pretracheal and preaortic nodes
7	Subcarinal	Unchanged
8	Paraesophageal	Unchanged
9	Pulmonary ligament	Unchanged
10[1]	Hilar	Designation of 'hilar' dropped because of ambiguity of the radiologic use of this term; renamed peribronchial on the left and tracheobronchial on the right; this station is now outside the pleural reflection
11	Interlobar	Reclassified as intrapulmonary
12	Lobar	Included in station 11
13	Segmental	Included in station 11

[1] Critical modifications that are being suggested.

Prognostic Significance of Lymph Node Metastases

Review of the surgical literature reveals conflicting reports of the prognostic significance of hilar nodes. Nohl [10] and Bergh [11] demonstrated that positive segmental and interlobar nodes do not appreciably influence prognosis. Similar observations were made by the Lung Cancer Study Group [12]. In their study, there was no significant difference in the recurrence rate per person per year (or death rate per person per year) whether or not pulmonary or hilar

Table 7. Site of lymph node involvement relationship to survival [from 13]

Metastasis	Five-year survival, %		
	squamous	adenocarcinoma	other
None	43.3	34.8	31.6
Lobar	22.5	15.3	16.2
Hilar	19.9	15.9	10.3
Mediastinal	11.5	2.9	6.1

Table 8. Number of failures (%) according to nodal involvement [from 15]

Nodal status	Patients, n	Failures (%)
No positive nodes	286	79 (27.6)
Intrapulmonary	91	32 (35)
Lung hilar	23	15 (65)

nodes harbored metastatic disease. On the other hand, Shields [13] reported a significant decrease in survival when lobar/hilar nodes contained malignancy (table 7). The controversy goes even further when various histologies, T stages, and locations of the nodes within the 'N1 region' are taken into account. In a report by the Lung Cancer Study Group [14], the presence of N1 had no impact on survival for squamous cell carcinoma, whereas it resulted in a significant decrease in survival in nonsquamous or mixed disease [12]. The Ludwig Cancer Study Group [15] reported a significant increase in failure rates when hilar nodes were involved as opposed to intrapulmonary nodes (table 8).

There is, however, unanimous agreement on the negative prognostic significance of mediastinal node metastasis. Nohl [10] and Bergh [11] reported 4-year survival rates of 42 and 49%, respectively, following pulmonary resection when the mediastinum was free of tumor metastasis. Survival rates fell to under 10% when upper mediastinal metastases were present. Similar observations were made by Shields [13]. Overall, review of large series reveals that metastases to various lymph node stations are indicative of further progression of lung cancer and have various degrees of negative prognostic significance (table 9) [1, 2].

Table 9. Cumulative percentage surviving 5 years and median survival by clinical and surgical TNM subsets [modified from 1]

TNM subset	Clinical			Surgical		
	n	% surviving	median survival months	n	% surviving	median survival months
T1 N0 M0	591	61.9	60–	429	68.5	60–
T2 N0 M0	1,012	35.8	26	436	59.0	60–
T1 N1 M0	19	33.6	20	67	54.1	60+
T2 N1 M0	176	22.7	17	250	40.0	29
T3 N0 M0	221	7.6	8	57	44.2	26
T3 N1 M0	71	7.7	8	29	17.6	16
Any N2 M0	497	4.9	11	169	28.8	22
Any M1	1,166	1.7	6	–	–	–
Total	3,753			1,436		

Irradiation of Lymphatics in Lung Cancer

Because of the negative prognostic impact of lymph node involvement in lung cancer, inclusion of lymph-draining areas has always been recommended in its radiotherapeutic management. The volume to be treated and the configurations of the radiation portals are determined by the size and location of the primary tumor, its drainage pathways (fig. 1, 2) and histology, as well as the technical expertise and availability of equipment. Inclusion of the primary imaged tumor with a 2-cm margin and the potential lymphatic drainage areas (fig. 1, 2) with a 1-cm margin are generally recommended.

When portals are designed to cover the potential lymphatic drainage, the following general principles are recommended. For primary tumors located in the upper lobes, the ipsilateral supraclavicular region, upper mediastinum, and subcarinal area should be included. The inferior margin of the portal should be 5–6 cm below the carina. Inclusion of the contralateral hilum, which once was a common practice, has no scientific basis. Inclusion of the contralateral supraclavicular area is still controversial. For primary tumors in the middle and lower lobes, the entire mediastinum is included in the irradiated volume with the lower border at the level of the diaphragm. Supraclavicular nodal regions do not need to be included in the irradiated volume unless substantial upper mediastinal lymphadenopathy is present. For the group of primary tumors located in the superior sulcus, inclusion of the ipsilateral supraclavicular nodal area is mandatory; inclusion of the contralateral supraclavicular area is contro-

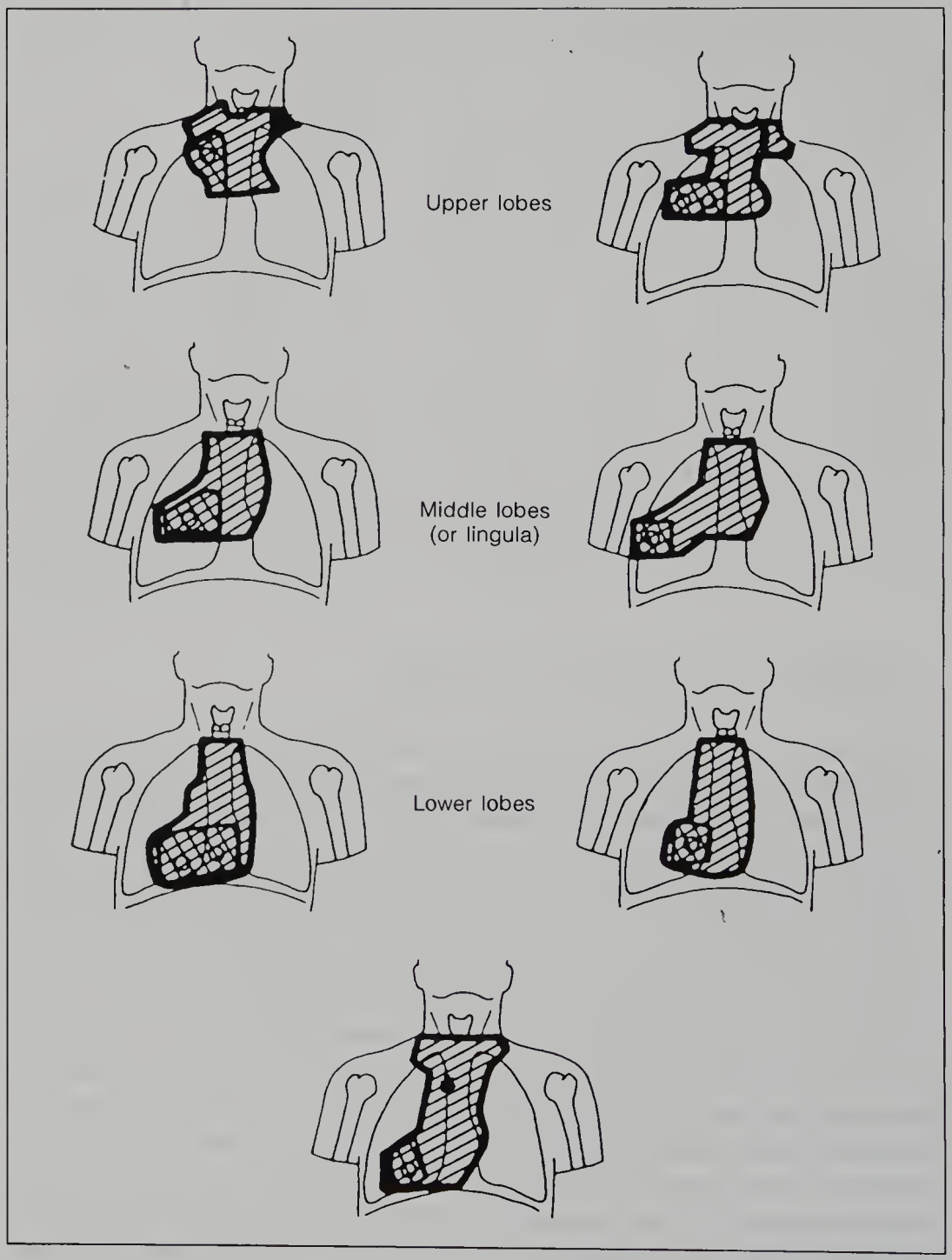

Fig. 4. Examples of portals used for irradiation of non-small cell carcinoma of the lung, depending on the anatomic location of the primary. The tumor and grossly enlarged lymph nodes are treated to higher doses (cross-hatched pattern). Inclusion of contralateral supraclavicular region is controversial (see text) [20].

versial but probably not needed. The lower border of the mediastinal portal in this group of patients – whether subcarinal nodes should be included – is controversial (fig. 4). The usual recommended dose for lymphatic drainage areas is 5,000 cGy at the rate of 200 cGy/day [16].

Results

The specific impact of irradiation of the lymphatics in the management of inoperable lung cancer is hard to assess. Although inclusion of these potentially involved areas in the radiation therapy volumes is common medical practice, there is little information on the frequency of failure in nodal areas alone, in the absence of failure at the primary site, after radiotherapy. Analyses often report the failure rates in 'irradiated lung' or 'within the irradiated volume'; even more often failure rates are reported under the umbrella of 'locoregional' [17, 18]. Three important reasons for this lack of information are: (1) postradiation changes on x-rays and CT scans in the lung parenchyma and mediastinum preclude precise interpretation and separation of radiation fibrosis from recurrent tumor in a specific site; (2) poor local control rates at the primary tumor site with radiation alone in patients with inoperable non-small cell lung cancer place the issue of tumor contol in lymph nodes at a lesser degree of importance and (3) it is a general belief that control of nodal metastasis by irradiation can be achieved with a higher degree of success than that of the primary tumor [19] and thus has received less attention.

Postoperative Radiation Therapy of Lymphatics

A great deal of controversy exists regarding the role of postoperative therapy in lung cancer. Retrospective institutional reports suggest a beneficial effect [16, 20, 21], but data from well-controlled prospective randomized trials proving its efficacy are few (table 10) [22]. It is generally agreed that in patients with complete tumor resection, clear surgical margins, and no nodal metastasis, postoperative radiation therapy is not indicated. In a randomized study by Van Houtte et al. [23] in which patients with complete tumor resection and no nodal metastasis were randomized to receive 6,000 cGy postoperatively or to be observed, there was no beneficial effect of postoperative radiation therapy. In fact, the group irradiated had worse survival, which may be attributed to complications of high-dose radiation therapy.

Results on the efficacy of postoperative radiation therapy in patients with N1 disease are conflicting. Martini et al. [24] reported on 75 patients with T1 N1 and T2 N1 disease who had complete, potentially curative resection with

Table 10. Lung cancer: survival after postoperative irradiation in patients with hilar-mediastinal lymph node involvement

Study (first author)	Total dose Gy	Histology	Surgery		Surgery + radiation		Survival end-point, years
			pts n	survival %	pts n	survival %	
Bangma [39]	45	All histologies	37	67	36	53	1
Choi [40]	40–56	Squamous cell carcinoma	29	33	46	33	5
		Adenocarcinoma	21	8	40	43	
Chung [41]	46	Squamous cell carcinoma	18	16	19	52	3
		Adenocarcinoma	7	0	14	28	
Emami [42]	50–60	All histologies			69	40	3
Green [43]	50–60	Squamous cell carcinoma	16	6	28	21	5
		Adenocarcinoma	6	0	16	62	
Herskovic [44]	60	Squamous cell carcinoma			28	44.6	2
		Adenocarcinoma			37	43.1	
Israel [45]	50	Squamous cell carcinoma	126	50	104	70	3
Kirsh [46]	50–55	Squamous cell carcinoma	10	0	50	36	5
		Adenocarcinoma	10	0	55	12	
Martini [27]	40–45	Squamous cell carcinoma			25	44	3[1]
		Adenocarcinoma			44	56	
Pavlov [47]	45	All histologies	301[1]	24	212	38	5
Van Houtte [22]	55–60	Squamous cell carcinoma			60	21	5[1]
		Adenocarcinoma			21	17	

[1] Patients treated with combination of surgery and chemotherapy.

mediastinal lymph node dissection. Of these, 10 patients received postoperative radiation therapy. No information was given on the radiation therapy dose, volumes, or technique. There was no difference between the nonirradiated and the irradiated groups in local control (11 and 10%, respectively) or survival (50 and 40%, respectively). The authors' conclusion was that no effect of radiation therapy on locoregional recurrence was noted. If patients with bad prognostic signs were assigned to receive irradiation, as indicated in their article [24], these results are open to alternate interpretation. Martini et al. [25], in an update of the same material 9 years later, reported on 214 patients with stage II non-small cell lung cancer. Forty-eight patients (22%) with worse prognostic factors (as indicated in the text) received postoperative radiation therapy. Again, there was no indication of the dose, fractionation, total time, or technique of the radiation therapy given. These authors indicated that patients with worse prognostic factors received postoperative radiation therapy, which often had not been a planned course after resection. They reported 5-year

survival rates of 45 and 13% for surgery alone and surgery plus postoperative irradiation, respectively. On the other hand, Ferguson et al. [26] reported on 34 patients with T1 N1 and T2 N1 non-small cell carcinoma of the lung. Eleven patients were treated with resection alone, and 23 patients received postoperative radiation therapy. Their report indicates 10% survival for patients having surgery alone versus 40% for patients receiving postoperative adjuvant therapy. The causes for these discrepancies will be discussed later.

The impact of postoperative radiation therapy in patients with positive mediastinal nodes is also controversial [27–29]. In a report by Martini et al. [27] on 445 patients with lung carcinoma with mediastinal lymph nodes, 80 patients had complete, potentially curative resection of the primary tumor and all accessible mediastinal lymph nodes. Sixty-eight of these patients received postoperative radiation therapy of 4,000–4,500 cGy. They reported a 49% 3-year survival in this group of patients. The authors conclude that patients with mediastinal nodes should receive postoperative radiation therapy. The Lung Cancer Study Group conducted a prospective randomized study in patients with stage II and III epidermoid carcinoma only; treatment was with surgery alone or surgery plus postoperative radiation therapy. 230 patients were assigned in this protocol. The dose of radiation was 5,000 cGy, delivered with a combination of parallel opposed and anterior and posterior oblique fields. Their report indicates a significant reduction in the local recurrence rate from 41 to 3% ($p<0.001$). There was no difference in 5-year survival between the two groups. It is important to note that only patients with epidermoid carcinoma were accrued in this protocol. Moreover, 25% of patients in the radiation therapy arm did not receive the prescribed dose of radiation.

Discussion

Potential areas of controversy regarding the results of postoperative radiation therapy in lung cancer are shown in table 11. As discussed earlier, the potential effect of patient selection for specific treatment programs is one of the most important deficiencies in these studies. Usually, patients with worse prognostic signs were treated with postoperative radiation therapy [24, 25], and the results compared with those from patients with better prognostic factors who did not receive postoperative irradiation.

The second factor is the lack of uniformity in anatomic description of nodal regions. Nodal stations, as outlined in figure 3, are accepted by most, but not all, thoracic surgeons but have been employed by few radiation oncologists. One of the most misunderstood areas is the term 'hilar nodes'. Although the AJC Manual for Staging applies this terminology strictly to nodal station 10, it

Table 11. Causes of controversy in the literature on postoperative radiation therapy in lung carcinoma

Lack of proper patient selection in retrospective studies (patients with worst prognostic factors are usually irradiated)
Lack of uniformity in anatomic description of nodal regions
Lack of uniformity of nodal surgical resection (sampling versus stripping)
Lack of pathologic description of degree of lymph node involvement (intracapsular versus extracapsular invasion)
Lack of uniformity in radiotherapeutic target volume delineation
Lack of uniformity in irradiation dose
Lack of rigid radiation therapy technique quality control
Lack of well-designed, prospectively controlled randomized studies of surgery versus surgery plus postoperative radiation therapy in patients with N1 and N2 disease

is often used for a mix of stations 4, 10, 11, and 12. In some publications, nodal station 10 has occasionally been applied to the nodes outside the pleural envelope contrary to its intended description. In addition, segmental nodes (nodal station 13) are often considered by radiotherapists as part of N0, whereas in the official staging system it is included in N1. It is very unlikely that postoperative irradiation will be of any value in patients with positive nodal station 13, whereas the likelihood of benefit does exist in patients with positive nodal station 10.

Recent surgical literature contains analysis of survival according to the specific level of mediastinal node metastasis, as well as the number of levels involved [25, 30]. Martini et al. [25] reported a 45% 5-year survival when a single level (of N1 node) was involved in comparison with 31% when multiple levels harbored metastasis. The difference was significant ($p = 0.016$). In a report by Regnard et al. [30], there was a 34% 5-year survival after surgery when lower tracheal nodes were involved compared with 18% when subcarinal nodes were involved. This difference was statistically significant ($p<0.005$). Additionally, they reported a 24% 5-year survival in patients with one level of positive nodes as opposed to 10% with more than one level. There is no such analysis in the literature dealing with postoperative radiation therapy. One could conceivably argue that the potential benefit of postoperative radiation therapy would be more apparent when more than one level of mediastinal nodes harbored metastatic disease.

Table 12. Impact of extent of surgery on lung carcinomas with mediastinal node metastasis

Study (first author)	Five-year survival, %	
	surgery sampling	surgery stripping
Nohl-Oser [48]	10	
Green [43]	6 (squamous cell carcinoma) 0 (adenocarcinoma)	
Paulson [49]	7	
Mountain [50]	8	
Choi [40]	8 (adenocarcinoma)	
Kirsch [46]	0	
Chung [41]	15 (squamous cell carcinoma) 0 (adenocarcinoma)	
Mountain [51]		17
Naruke [52]		19
Lung Cancer Study Group [15]		23

The third area of potential controversy is the extent of nodal resection at the time of thoracotomy. Although some surgeons prefer sampling of grossly palpable (suspicious) nodes, others have preferred complete surgical stripping of the mediastinal nodes. Table 12 reveals significant improvement in survival with more extensive surgical excision of mediastinal nodes.

The fourth area of controversy is the lack of precise pathologic description of the degree of invasion of the node by the tumor. Larsson [31] reported a significant difference in survival between patients whose mediastinal nodal metastasis did or did not have extracapsular extension at the time of pathologic examination (fig. 5). Again, there is no such analysis in the literature of patients treated with postoperative radiation therapy. One could make a reasonable argument that extranodal extension is a definite indication for postoperative radiation therapy. Similar practice is currently routine in cancers of the head and neck.

Most of the literature reporting on postoperative radiation therapy in lung cancer has few if any details on radiation treatment in regard to total dose, fractionation, duration, and quality control aspects of therapy. Doses have varied from 3,000 cGy in 3 weeks [29] for N2 disease to 6,000 cGy [23] for N0 disease. The dose in the former study appears to be inadequate; from the analysis by Emami et al. [32], the minimum required dose for controlling nodal disease appears to be 5,000 cGy. There is no uniformity in the definition of the target volume in the irradiation of nodal disease in lung cancer. While many

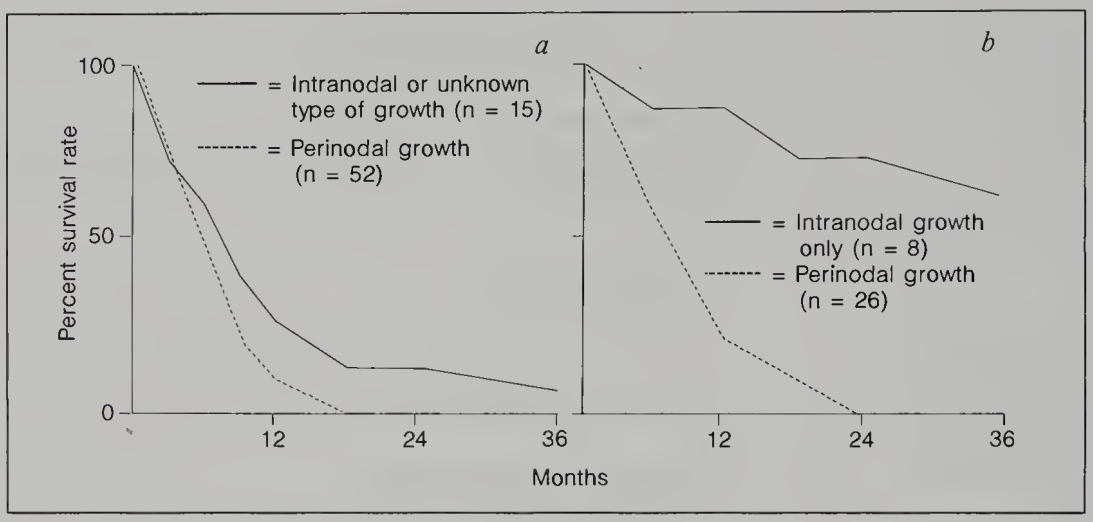

Fig. 5. a Prognostic significance of the type of the mediastinoscopically detected ipsilateral lymph node metastases in patients not submitted to surgery. *b* Prognostic significance of the type of the mediastinoscopy detected ipsilateral lymph node metastases in resected patients (operative deaths included) [from 31].

radiotherapists recommend inclusion of the contralateral hilum and contralateral supraclavicular region in the irradiated volume, there are few data to support this pratice. Robinow et al. [33] and Turrisi [pers. commun.] reported 0% failure in 101 patients in which the radiographically uninvolved contralateral hilum was not included. Information on the technical quality of delivery of radiation is almost nonexistent in most studies. Analysis by Emami et al. [32] has shown that the adequacy of coverage of the target volume by the prescribed dose has a significant impact on both local control and survival. (In that study, if 95% of the prescribed dose covered at least 95% of the intended target volume, the delivery of radiation was considered adequate.)

Finally, the lack of properly designed randomized studies, with proper stratification on the factors listed above and with predetermined quality assurance criteria for both surgery and radiation therapy, are the main reasons why definitive answers regarding the utility of adjuvant irradiation are not yet available. Such insights may be on the horizon, as important protocol studies addressing these issues are underway by the RTOG and other major investigation groups.

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Upper Gastrointestinal Cancers: Rationale, Results, and Techniques of Treatment

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The intent of this chapter is to discuss indications for and results of lymphatic treatment for upper gastrointestinal (GI) malignancies (esophagus, stomach, pancreas, and biliary). No randomized trials in upper GI cancer have addressed the extent of irradiation fields with regard to inclusion versus exclusion of nodal sites. Therefore, the rationale for nodal irradiation is based on patterns of failure after surgical resection utilizing autopsy, reoperation, and clinical analyses.

With gastric and other upper GI sites, lymph node involvement per se does not necessarily imply distant metastasis and poor survival. Node-positive gastric cancer patients with primary lesions confined to the wall have a prognosis similar to that of node-negative patients with lesions extending beyond the wall.

Imaging of nodal spread is unsatisfactory and limited to computed tomography (CT) evidence of nodal enlargement at either initial workup or subsequent follow-up. Metastatically involved nodes often are not definitively enlarged (in esophageal cancer, they are rarely ≥ 1.0 cm), explaining the poor predictive value of CT and MRI [1]. With esophageal cancers, however, transluminal ultrasound (US) is also available as a diagnostic tool: the accuracy of CT is usually $\leq 50\%$, but modern US series report accuracy rates of 80–95% [2]. The only procedure with accuracy routinely $\geq 90\%$ is surgical exploration with resection or biopsy. Therefore, the best data concerning nodal patterns of failure after initial treatment are from autopsy and reoperative series.

Table 1. Esophageal carcinoma lymph nodes at diagnosis[1] [modified from 4]

Nodal group	Tumor location, %		
	upper	middle	lower
Thorax			
Upper	29	11	10
Middle	27	21	14
Lower	29	18	27
Abdominal	32	35	70
Total	67	51	71

[1] SCV nodes not routinely sampled; n = 600.

Esophagus

Direct and Lymphatic Spread and Associated Anatomy

The esophagus lies in close proximity to a number of vital structures in the neck and mediastinum. Once extension beyond the esophageal wall occurs, good radial resection margins are uncommon. Even with lesions limited to the esophageal wall, total removal of tumor may be difficult in view of tumor spread longitudinally (along mucosal layers, intermuscular spaces, and submucosal lymphatics), multicentric lesions and skip metastases. The longitudinal growth pattern accounts for the 10–15% of esophagectomy specimens with positive margins, and for the predisposition of this tumor to relapse at the margins of surgical resection or irradiation fields.

Lymph node involvement is found in the overwhelming majority of patients with carcinoma of the esophagus [3–5]. The main nodal areas at risk include the cervical, supraclavicular, mediastinal, and subdiaphragmatic areas (celiac axis, perigastric), although distribution of nodal involvement varies with the site of origin (table 1). Nodal mapping data also indicate that supraclavicular nodes are involved in 20–30% of patients and are usually nonpalpable [4, 5]. Neck or abdominal nodal involvement is not uncommon with an esophageal primary at any site.

Patterns of Failure

Local-regional relapse (or persistence) and distant metastases are both extremely frequent after any treatment approach (table 2). Autopsy series in untreated patients reveal nodal involvement in 80–85% and cancer restricted to the local-regional area in about one-third. Modern autopsy series [6–8] demon-

Table 2. Clinical failure patterns in esophageal carcinoma

Treatment modality	Series analyzed, n	Total patients, n	Site of relapse, %		
			primary	mediastinum/ neck	DM[1]
Irradiation (XRT)	6	1,382	56–85[2]	10–43	36–50
Surgery	5	729	8–50[3]	40–50	17–69
Surgery +/– XRT[4]	3				
			locoregional		DM[1]
1. Surgery		189	30; 67; 52		46; 50
2. Pre- or postop XRT[5]		156	15; 46; 48		52; 50
XRT +/– Chemo	2				
1. XRT		93	62; 84		40; 23
2. XRT + Chemo		89	44; 61		23; 32

[1] Distant metastases.
[2] 25% in stage I.
[3] Primarily anastomotic failures; anastomotic failures correlated with longitudinal margins of resection (1 series).
[4] Randomized trials only; each randomized group is paired by vertical line.
[5] Anastomotic failures 4 vs. 13% without preop XRT (1 series); regional nodal failure 40% overall in both preop and surgery only (1 series).

strate the problem with distant metastases (chiefly lung/pleura, liver and bone) as well as local-regional recurrence; the latter occurs as the only failure in 25–40% of patients.

In irradiation only series, local-regional disease is the dominant clinical problem and site of relapse (table 2) [7–9]. Although Pearson's [9] results with irradiation alone surpass other published results, 80% of his radically irradiated patients failed to survive 5 years, and approximately half died from local recurrence.

Evaluations of failure patterns after surgical resection and adjuvant treatment also reveal a high incidence of local-regional failure (LF-RF) (table 2) [8, 10]. This is due to tumor bed relapse, anastomotic recurrence and progression in dissected or undissected nodal regions. While surgery alone can yield excellent survival in those few patients with a superficial lesion and uninvolved nodes [11] (table 3), the majority of resected patients have extension beyond the wall, nodal involvement, or both; 5-year survival is usually $\leq 15\%$.

In a recent trial by the Japanese Esophageal Oncology Group [10], 258 patients were randomized to postoperative irradiation versus chemotherapy (cisplatin plus vindesine) following curative resection. The surgery involved a

Table 3. Results by T and N stage in surgically treated esophagus cancer, Mayo Clinic [modified from 11]

TNM stage[1]	Patients, n	5-year survival, %
$T_1 N_0 M_0$	7	86
$T_2 N_0 M_0$	11	34
$T_2 N_{1-3} M_0$	15	15
$T_3 N_0 M_0$	14	
$T_3 N_{1-3} M_0$	53	

[1] 1983 American Joint Committee Staging System [American Joint Committee, Esophagus; in Beahrs OH, Myers MH (eds): Manual for Staging of Cancer, ed 2. Philadelphia, Lippincott, 1983, pp 61–66].

complete resection of the primary tumor as well as dissection of regional nodes (mediastinal, perigastric, and celiac). In the adjuvant irradiation arm, the upper mediastinum and supraclavicular region were treated to a dose of 50 Gy in 25 fractions over 5 weeks. Both groups had a high incidence of relapse in the mediastinum or neck (23 mediastinum and 8 neck relapses in unirradiated patients versus 17 and 5 in irradiated patients). Other randomized trials of preoperative [12, 13] and postoperative irradiation [14] show consistent reductions in LF-RF, but the magnitude of such is insufficient to impact on survival.

For unresected lesions, the combined chemoradiotherapy approach has improved both local control and survival in nonrandomized [15, 16] and randomized trials [17–19]. In an RTOG trial [18], patients were randomized to irradiation plus 5-FU/cisplatin (50 Gy in 25 fractions over 5 weeks) versus irradiation alone (64 Gy in 32 fractions). Actuarial 2-year survival was 42 versus 10% ($p = 0.0009$), and actuarial 2-year local control was 53 versus 30% ($p = 0.01$) with the advantage to the combined modality approach. Since approximately 50% of patients failed within irradiation fields even with combined modality treatment and 23% developed distant disease, future trials will address both an increase in irradiation dose as well as more intense chemotherapy. In the RTOG trial, nodal groups were included to 50 Gy in the irradiation alone patients (plus 14 Gy primary boost) versus 30 Gy with combined irradiation plus chemotherapy (plus 20 Gy primary boost). The initial treatment field extended from the supraclavicular fossa to the esophagogastric junction except in lower third lesions where inclusion of the supraclavicular region was optional. With regard to LF-RFs, no distinction was made between primary versus nodal relapse.

Radiation Field Design

Radiation fields and doses have varied widely from institution to institution. Techniques vary according to upper dose levels and include parallel opposed fields, rotation, single anterior/two posterior oblique fields or four fields with AP:PA plus laterals (fig. 1). Curative strategies for radiation alone have ranged from Pearson's 7×14 cm average portal to that of the Stanford preoperative series by Guernsey et al. [5] who recommended inclusion of the entire esophagus as well as supraclavicular and infradiaphragmatic node systems due to the possibility of extensive submucosal and/or nodal spread. They delivered 66 Gy over 7 weeks preoperatively to the primary lesion with a 6-cm margin in most patients and as high as 61 Gy to the nodal areas if the preirradiation laparotomy revealed involved nodes. In the Stanford series, however, 5 patients died as a direct result of irradiation: cardiac deaths in 3 and pulmonary-related problems in 2.

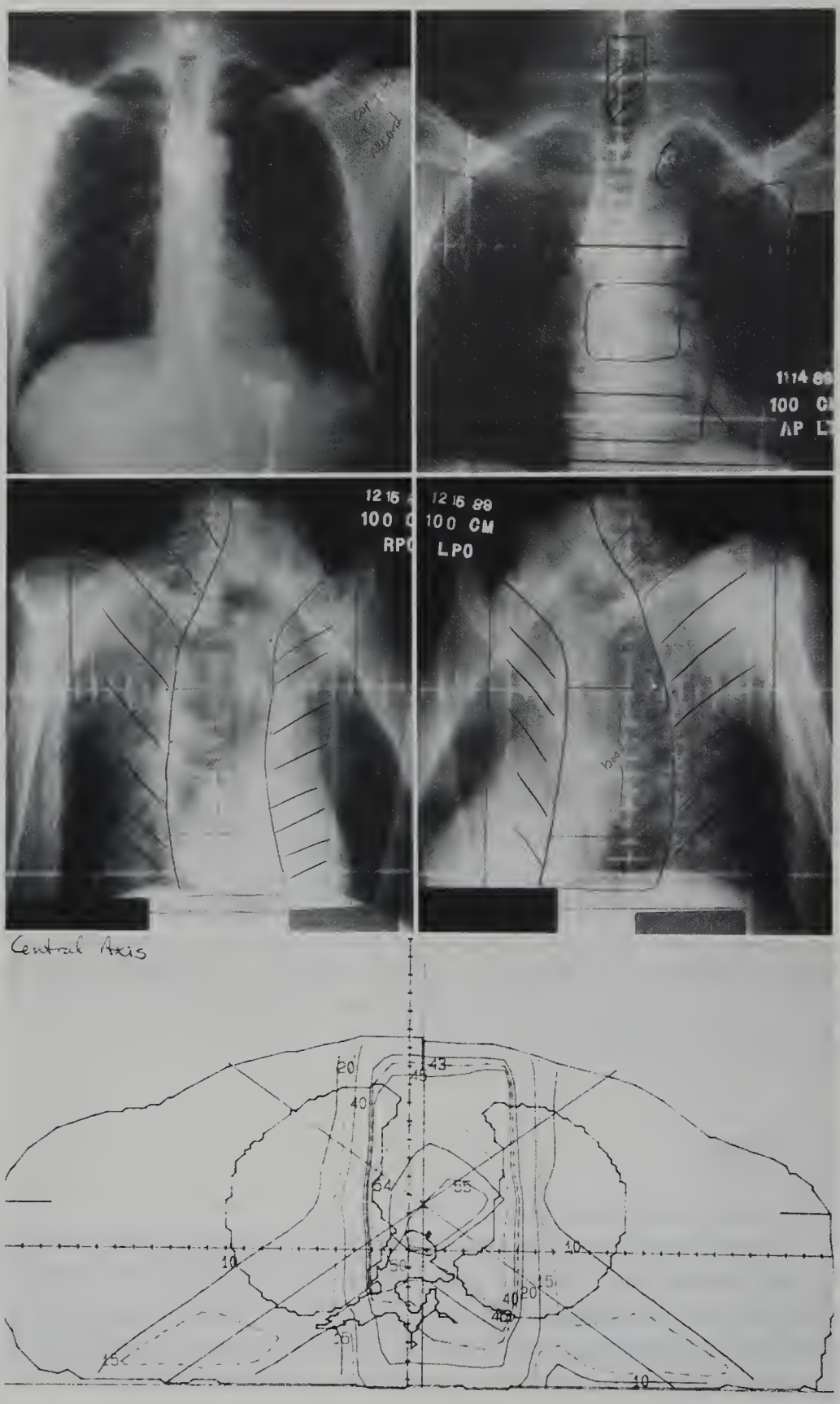
Currently, intergroup phase 2 chemoradiotherapy trials are utilizing fields which encompass the primary tumor with initial esophageal margins of at least 5 cm. After a dose of 45–50 Gy, fields are reduced to tumor plus 2 cm, and the boost field dose is carried to 60–64.4 Gy. The objective of these trials is to test the feasibility of high-dose irradiation in combination with chemotherapy, which could then be compared against the current standard of 50 Gy plus chemotherapy in a phase 3 trial. As noted previously, extended fields were used in the positive RTOG trial.

At present a high percentage of patients still have persistence or relapse of the primary lesion. Until better local control can be achieved, it will be hard to determine the relevance of lymphatic irradiation, dose levels necessary for nodal regions, etc. This information may be more easily collected in an adjuvant setting where the addition of surgery should improve the ability to control the primary lesion. In that regard the Japanese Esophageal Oncology Group has been encouraged to evaluate combined postoperative irradiation plus chemotherapy as a result of positive RTOG and ECOG randomized trials for unresected disease.

Gastric

Direct or Lymphatic Tumor Spread

Both direct tumor extension and lymphatic spread present problems for the surgeon with regard to achieving complete resection of gastric cancers with good margins. Abundant lymphatic channels exist within the gastric wall in both the submucosal and subserosal layers. Microscopic and subclinical intramural spread away from the gross lesion through these pathways occurs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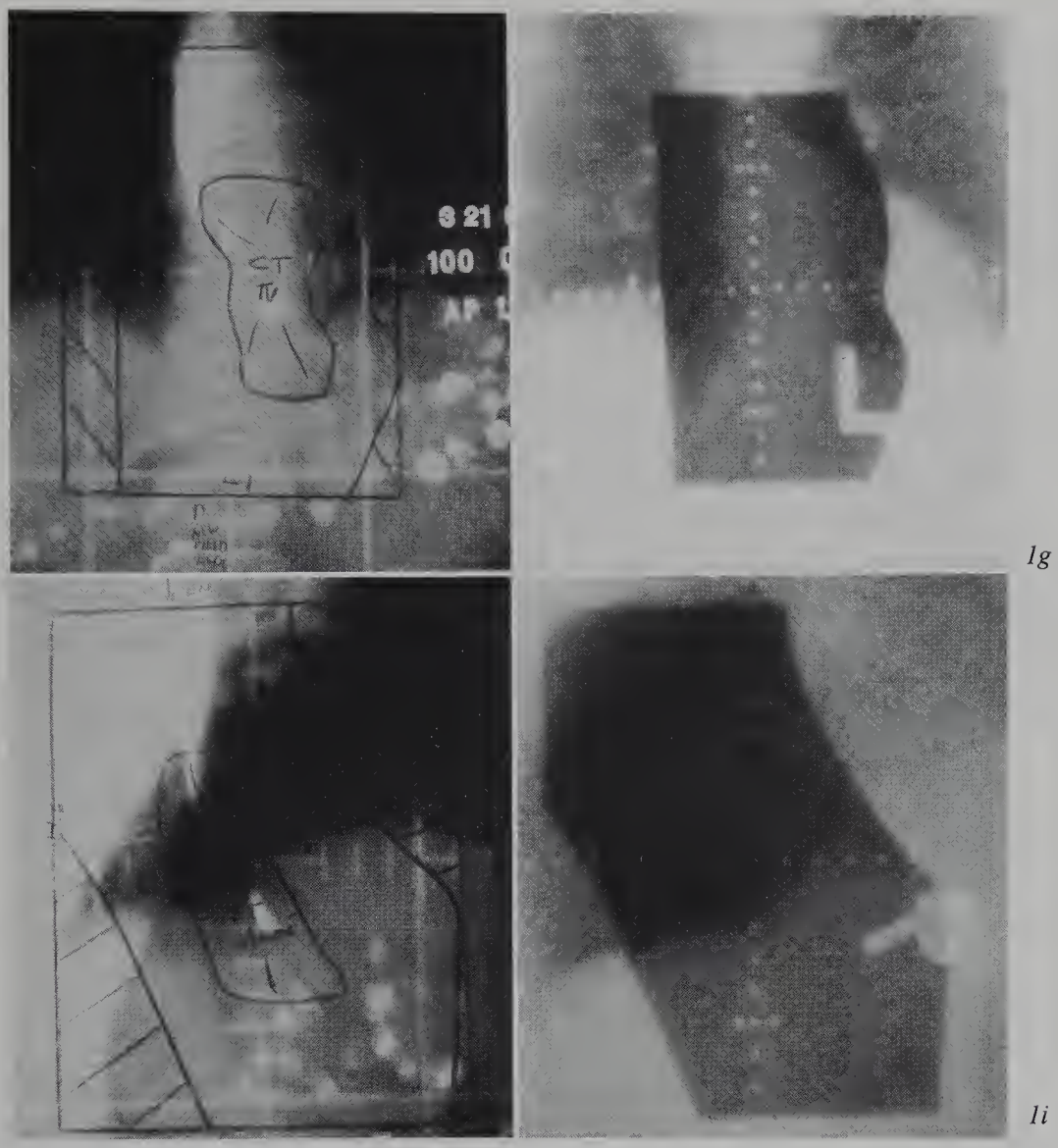


Fig. 1. Irradiation techniques for esophageal cancer. (1) Three-field technique of single anterior plus paired posterior obliques for patient with mid-thoracic primary. *a* Barium swallow demonstrating lesion. *b–d* Irradiation fields. *b* Anterior large plus boost field; *c, d* Paired posterior obliques. *e* Isodose curve at isocenter. (2) Four-field technique of AP:PA plus paired laterals for patient with distal esophageal lesion. *f, g* AP:PA simulator and portal films. *h, i* Lateral simulation and portal film demonstrate ability to spare some heart with lateral fields.

frequently, and can mislead the surgeon into thinking that tumor margins are adequate. This submucosal plexus continues through the esophagus and can lead to extensive proximal spread. Although a so-called 'duodenal block' occurs, with the mucosa scarcely ever being involved for more than 1–2 mm

Table 4. Gastric cancer: T-stage versus incidence of node involvement and survival

Primary T stage	5-year survival, %	
	nodes negative	nodes positive
T_1 (mucosa or submucosa only)	85–100	40–50
T_2 (beyond submucosa, within wall)	50–60	40–50
T_3 or T_4 (through gastric wall)	40–50	5–20

beyond the pylorus, a prominent subserosal plexus exists in the duodenum and allows distal spread in as many as 30–40% of patients.

There are numerous pathways of lymphatic drainage from the stomach which make it difficult to accomplish a complete lymph node dissection. Although the primary drainage is usually to lymph nodes along the lesser and greater curvatures (gastric and gastroepiploic nodes), tumor can also spread to nodes of the entire celiac axis (porta hepatis, subpyloric, gastroduodenal, splenic-suprapancreatic, retropancreaticoduodenal) and distal paraesophageal systems.

Patterns of Failure – Surgery Alone

Surgery remains the mainstay of treatment for this malignancy, but over the past three decades has done little to alter the course of the disease. Although resectability has increased from about 30% in the 1940s to 50–60% at present, cure rates by extent of disease have changed only slightly [19, 20] (table 4). Local regrowth, failures in the regional lymph nodes, and distant failures via hematogenous or peritoneal routes are all common mechanisms of relapse after 'curative' resection.

The magnitude of LF-RF has been demonstrated in reoperation, autopsy, and clinical series [19–23]. The relapses were primarily in organs and structures of the gastric bed and lymph nodes, with a smaller but significant number of failures in the anastomoses, gastric remnant or duodenal stump (table 5). In a more recent autopsy analysis from the University of Washington [22], failure patterns were analyzed in 85 patients who died of gastric cancer: in the 16 patients who underwent a potentially curative resection, 15 (94%) had a LF-RF component.

In the reoperative analysis by Gunderson and Sosin [21], initial treatment was surgery alone without any pre- or postoperative adjuvant therapy. The operative procedure utilized was at the discretion of the surgeon, with a large group of patients having splenectomy, omentectomy, and radical lymph node dissection in addition to some form of gastrectomy. LF-RF occurred as the only failure in 29% of the 86 patients with relapse and as any component of failure in 88%. Extent of the initial operative procedure had little if any effect on either the incidence or type of subsequent failure (table 6). Subsequent relapse in the

Table 5. Gastric cancer: patterns of LF-RF after surgical resection in clinical, reoperation, and autopsy series [from 20, with permission]

Failure area	Incidence (any component)							
	MGH clinical (n = 130)		Univ. Minn. reoperation (n = 105)		McNeer et al. autopsy (n = 92)		Thomson and Robins autopsy (n = 28)	
	n	%	n	%	n	%	n	%
Gastric bed	27	21	58	55	48	52	19	68
Anastomosis or stumps	33	25	28	27	55	60	15	54
Abdominal or stab wound	–	–	5	5	–	–	–	–
Lymph node(s)	11	8	45	43	48	52	–	–

Table 6. Extent of gastrectomy and node dissection versus type of LF-RF – University of Minnesota reoperation series [modified from 20]

Operative procedure	Any component of LF-RF[1]							
	failure/ total at risk n	gastric bed		anastomo-sis or stumps		abdomen or stab wound		nodes (LN)	
		n	%	n	%	n	%	n	%
Subtotal gastrectomy	53/72	36	50	18	25	3	4	29	40
Method 1	25/36	18	50	13	36	0	–	11	31
2	15/17	9	53	4	24	1	6	9	53
3	13/19	9	47	1	5	2	11	9	47
Total gastrectomy	27/33	20	61	8	24	2	6	15	45
Method 1	0	–		–		–		–	
2	14/15	10	67	5	33	1	7	11	73
3	13/18	10	56	3	17	1	6	4	22
Totals	80/105[2]	56	53	26	25	5	5	44	42

Method 1 (pre-1950): subtotal or total gastrectomy, regional node dissection.

Method 2 (1950–54): method 1 plus splenectomy, total omentectomy and additional node dissection (splenic/suprapancreatic, central celiac).

Method 3 (1954 on): methods 1 and 2 plus additional node dissection/porta hepatis and pancreatic duodenal with intent of total node dissection of all primary node areas equivalent to R_2 or R_3 dissection.

[1] Percent values represent patients at risk with complete follow-up.

[2] An additional 6 patients had failure, but only 80 of 86 were evaluable regarding both operative method and pattern of failure.

areas of initial node dissection occurred in a high percentage of patients who had intended radical lymph node dissections, indicating the difficulty of performing a complete dissection in this anatomic location. Any potential survival benefits seen with more extensive node dissections in nonrandomized analyses may have been due to the phenomenon of a shift in stage rather than superior surgery, since randomized trials to date have demonstrated no survival benefit [24].

Patterns of failure by stage were analyzed in detail in a series of 130 patients who underwent resection with curative intent at the Massachusetts General Hospital (MGH) [23]. LF-RF occurred as any component of failure in 49 patients (38%) and as the sole failure in 21 (16% of 130 at risk and 24% of the 88 with any disease relapse). The incidence of LF-RF by stage was in excess of 35% for modified Astler Coller Stages B_2, B_3, C_2, and C_3. Some additional information on patterns of relapse by stage exists in both the University of Minnesota reoperation analysis and the University of Washington autopsy analysis. Although anatomic sites of failure are more accurate in such analyses, patient selection is potentially biased since only a subset of patients who had curative resection had a subsequent reoperation or autopsy.

All these data suggest that the development of an effective therapy for local-regional disease as an adjuvant to surgery could potentially benefit at least 20% of patients. Effective systemic therapy is also essential.

Impact of Adjuvant Treatment on LF-RF

Randomized trials from Mayo Clinic [25] and from centers in the UK [26] suggest that adjuvant postoperative irradiation and chemotherapy may reduce LF-RF. In the Mayo Clinic trial, high-risk patients randomized to receive postoperative irradiation plus 5-FU had a 23% 5-year survival versus 4% in patients randomized to surgery alone ($p = 0.05$). Local failure appeared lower in patients who received adjuvant treatment (39 vs. 54%). In the British trial, no difference in survival was seen with the addition of single adjuvant arms of irradiation or chemotherapy versus surgery alone. The irradiation arm had the lowest incidence of LF-RF as the initial site of relapse: surgery alone – 36/145 (27%); surgery plus irradiation – 15/153 (10%) or plus chemotherapy 26/138 (19%).

Separate single institution analyses from MGH [27], Thomas Jefferson University Hospital (TJUH) [28], and the University of Pennsylvania [29] also suggest that combined adjuvant irradiation and chemotherapy may have an impact on local control and possibly survival. In an MGH analysis, the LF-RF rate in 14 patients who received postoperative irradiation plus chemotherapy after a potentially curative resection was 14% versus a $\geq$ 35% incidence in similar high-risk patients treated with surgery alone. Median and 4-year

survivals in the adjuvant group were 24 months and 40%. In the TJUH analysis, the LF-RF incidence with surgery alone was 45% (17/38), surgery plus chemotherapy – 54% (7/13), surgery plus radiation plus chemotherapy – 19% (3/16). Two-year local control for patients with negative resection margins was 93% in patients with adjuvant irradiation and chemotherapy versus 55% in unirradiated patients ($p = 0.03$). Patients with adjuvant treatment also had an apparent improvement in survival: in those with $T_{3,4}$ N(+) lesions, median survival was increased from 9 to 13 months, and 5-year survival from 4 to 22% ($p = 0.03$). In a University of Pennsylvania analysis, the incidence of LF-RF with surgery alone was 75% (31/40) versus 24% (4/17) with adjuvant radiation alone and 15% with radiation plus chemotherapy (4/27). Median survival in the latter group was 21 months versus 15 months with adjuvant irradiation alone.

A randomized intergroup trial is currently in progress in the United States to evaluate the impact of adjuvant tumor bed nodal irradiation plus chemotherapy on tumor control and survival in patients with complete resection and negative margins but at high risk for relapse. The control group is surgery alone. Parallel opposed or multiple fields are treated to 45 Gy in 25 fractions over 5 weeks; patients receive two cycles of bolus 5-FU plus low-dose leucovorin before, during, and after irradiation.

Design of Radiation Fields

The patterns of tumor bed and nodal failures in the University of Minnesota reoperative group [21] were in a distribution suitable for inclusion within a shaped radiation portal (fig. 2a), which should be modified depending on the initial extent of disease. In figure 2b these portals are superimposed on the limiting organs of tolerance. With accurate field definition, aided by clip placement in the splenic hilum and porta hepatis, one-half to two-thirds of the left kidney could be spared in many patients, and inclusion of the porta hepatis and retroduodenal nodal regions would include only a minor portion of the right kidney.

Dose-limiting organs and structures in the upper abdomen (stomach, small intestine, liver, kidneys, and spinal cord) are numerous. With properly shaped fields, doses of 45–50.4 Gy in 1.8–2.0-Gy fractions can be delivered with a $\leq 5\%$ risk of severe toxicity [30, 31]. In view of the posterior extent of the gastric fundus and medial left hemidiaphragm, it becomes impractical to routinely use lateral portals for a portion of treatment as is done in patients with head of pancreas cancers in order to spare spinal cord or kidney. Since parallel opposed portals are the most practical field arrangement for delivering most tumor nodal irradiation, one must limit either the volume of normal tissue included or the upper dose level. Multiple field techniques should be considered when this would improve long-term normal tissue tolerance. With lesions at the level of the esophagogastric

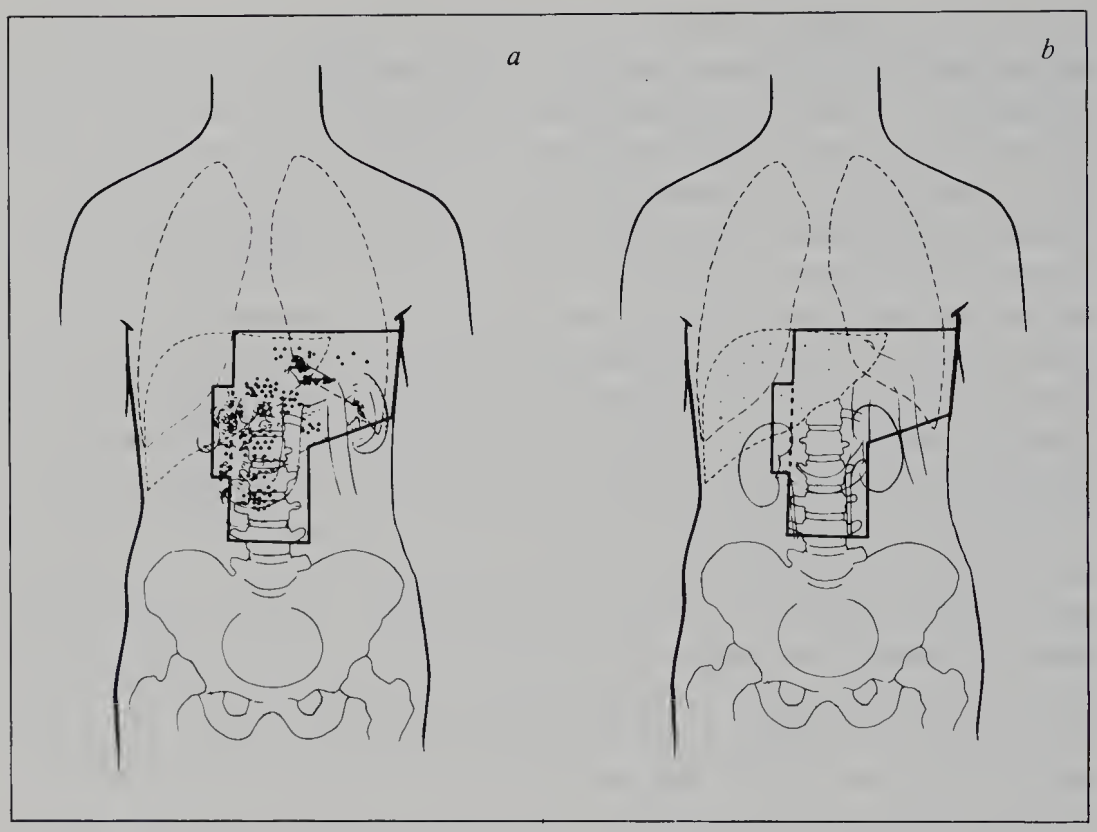


Fig. 2. Patterns of failure in the University of Minnesota gastric cancer reoperative series with superimposed idealized irradiation fields *(a, b)* and relationship to dose-limiting organs or structures *(b)*. ● = Local failures in surrounding organs or tissues; ○ = lymph node failures; * = lung metastases; · = liver metastases [from 20, p 772, with permission].

junction, if moderate lateral extension is noted on a preoperative CT or operative clip placement, lateral or obliqued fields can be used to decrease the volume of heart within the irradiation field (fig. 1).

Pancreas

Anatomy – Direct Extension or Lymphatic Spread

The pancreas has intimate contact with a number of surrounding organs which can be involved by direct tumor extension. The pancreatic lymphatics are very rich and have many connections with those of the duodenum. Primary drainage is to superior and inferior pancreaticoduodenal, porta hepatis and suprapancreatic nodes [32]. With posterior tumor extension, para-aortic nodes are at risk. When lesions originate in or involve the body or tail of the pancreas, splenic hilar nodes are also at risk.

Incidence of LF-RF with Surgery Alone

Little has been done to systematically analyze areas of relapse with pancreatic cancer, because most lesions are initially unresectable for cure. Relapse after curative resection was analyzed in a series of 31 patients from MGH [33]. Of the 26 postoperative survivors, 22 died of disease: the incidence of LF-RF was 50% (13/26) and liver metastases were also common. A more recent analysis from the University of Kansas [34] indicated similar local failure rates (50%) following resection, as well as a high incidence of liver metastases (44%) and peritoneal seeding (31%). It was not possible to distinguish tumor bed from nodal failures.

In some institutions, radical node dissections are being performed in an attempt to decrease the incidence of local-regional relapse and improve survival. As noted for gastric cancer, it will be difficult to perform a complete node dissection. In addition, tumor bed margins of resection will still be narrow in view of the proximity of the portal vein and superior mesenteric vessels posteriorly and medially.

Impact of Adjuvant Treatment on Survival and LF-RF

In patients with resectable lesions, there is justification for adjuvant treatment on the basis of patterns of failure after resection and the results of a prospective randomized trial from the Gastrointestinal Tumor Study Group (GITSG) [35]. In this study, patients were randomized to receive no further treatment (surgery alone control arm – 22 patients) or irradiation plus 5-FU (40 Gy in a 6-week split-course technique with 5-FU 500 mg/m^2 days 1–3 of each sequence followed by weekly 5-FU for 2 years – 23 patients). Fields were designed to include the tumor bed as well as major nodal areas at risk. A survival advantage was seen with the combined treatment, with nearly a doubling in median survival (20 vs. 11 months), a 2-year survival rate of 42 versus 15%, and a 5-year survival rate of 19 versus 5% ($p = 0.05$). Subsequently, the GITSG registered 30 additional patients to combined modality irradiation plus 5-FU and replicated the improved survival seen in the randomized trial [36].

The impact of treatment on the incidence of local failure was difficult to discern in the GITSG series. The incidence of local recurrence was high in both the surgery alone and adjuvant groups (33 and 45% of evaluable patients). With the low doses of irradiation used in this trial (40 Gy in 6 weeks + 5-FU), the adjuvant treatment did not appear to have a significant impact on local control. At the Mayo Clinic, higher doses of irradiation have been combined with 5-FU with an apparent improvement in local control when compared with GITSG data [37]. A four-field technique was used to deliver 45 Gy in 1.8-Gy fractions to a tumor bed nodal field, and 50–54 Gy to a tumor bed boost in a majority of

the 29 patients who received adjuvant treatment after gross total resection. A similar doubling in median and long-term survival was seen when compared with results achieved with surgery alone at that institution despite similar surgical techniques. LF-RF was documented in only 2 of 28 patients (7%) who had a curative resection followed by adjuvant irradiation plus 5-FU. Similarly, improved local control and survival was seen in the University of Kansas analysis when doses of 55–60 Gy plus 5-FU were compared to 45–54 Gy plus 5-FU [34].

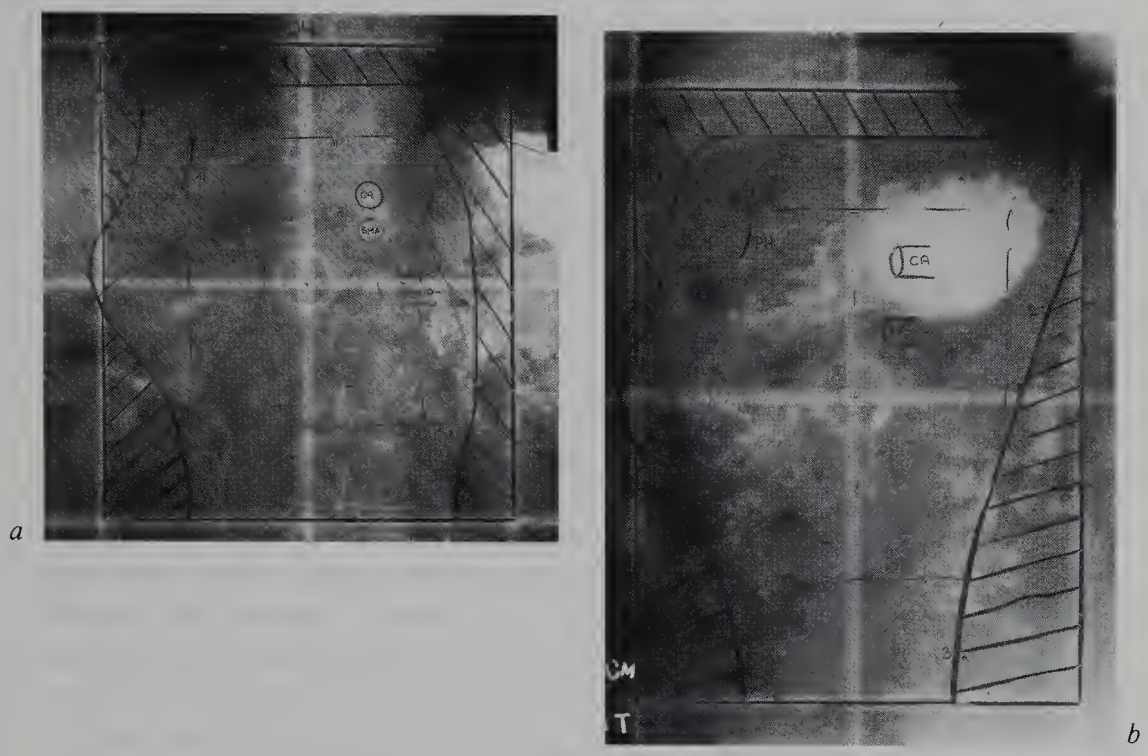
Design of Irradiation Fields

The intent of treatment is to use multiple-field fractionated external beam techniques with high-energy photons to deliver 45–50 Gy in 1.8-Gy fractions to unresected or residual tumor or tumor bed as defined by CT and clips, plus nodal areas at risk [38]. With head of pancreas lesions, major node groups include the pancreaticoduodenal, porta hepatis, celiac, and suprapancreatic. For unresected lesions, the latter node group is included along with the body of pancreas for a 3- to 5-cm margin beyond gross disease, but more than two-thirds of the left kidney should be excluded from the AP:PA field since at least 50% of the right kidney is often in the field because of duodenal inclusion. The entire duodenal loop with margin is included, since pancreatic head tumors may invade the medial wall of the duodenum and place the entire circumference at risk. The superior field extent is at mid- or upper-T11 vertebral body for adequate margins on the celiac vessels (T12, L1).

With unresected body-tail lesions, at least 50% of the left kidney may need to be included in order to achieve adequate pancreas margins and include node groups at risk (lateral suprapancreatic and splenic hilum). Since inclusion of the entire duodenal loop is not indicated with body or tail lesions, at least two-thirds of the right kidney can be preserved; with tailored blocks, one can usually cover pancreaticoduodenal and porta hepatis nodes adequately. The upper field extent is occasionally more superior with body lesions in order to obtain adequate margin on the primary lesion.

With the lateral fields, the anterior field margin is 1.5–2.0 cm beyond gross disease. The posterior margin is at least 1.5 cm behind the anterior portion of the vertebral body to allow adequate margins on para-aortic nodes which are a major node group at risk with posterior tumor extension in either head or body lesions. The lateral contribution is usually limited to 1,800–2,000 cGy or less because a moderate volume of kidney or liver may be in the field.

After resection, AP:PA and lateral fields are designed, as for unresected lesions, on the basis of preresection CT primary tumor volumes, operative clip placement, and postoperative CT nodal volumes (fig. 3) [20]. The only border that can be more restrictive is the anterior border on lateral fields, since the



a *b*

Fig. 3. Irradiation fields encompassing tumor bed and nodal regions at risk following resection of pancreatic cancer. *a* AP:PA. *b* Paired laterals [from 37, with permission].

primary tumor has been resected. This border is determined by vascular/nodal boundaries as demonstrated on CT (porta hepatis, superior mesenteric and celiac).

Biliary Tract

Anatomy and Tumor Spread – Direct Extension or Lymphatic

Both direct invasion of the liver and extension to involve the cystic and common ducts with resultant obstruction are common with gallbladder cancers. Lymphatic drainage is initially to cystic and common bile duct nodes and then to the pancreaticoduodenal system with later potential spread to the rest of the celiac axis or the superior mesenteric or aortic nodes. In combined series, regional lymph nodes were involved in 42 and 52% of patients at exploration and autopsy, respectively, and retroperitoneal lymph nodes in 23 and 26% [38].

Bile duct tumors can spread by a variety of mechanisms, but they most commonly do so by direct extension within the rich lymphatic network in the submucosa, by extraductal involvement of vascular structures within the porta hepatis or surrounding organs, or by metastasis to lymph nodes in the porta hepatis and celiac axis. The pancreaticoduodenal nodes are involved more frequently than with gallbladder primaries.

Patterns of Failure – Surgery and Adjuvant Treatment

Local recurrences in the tumor bed or regional nodes after 'curative' resection are common for both gallbladder and extrahepatic biliary duct lesions [38]. With bile duct cancer, proximal and distal margins are often narrow as are circumferential margins when lesions extend through the entire duct wall, and LF-RF is the usual cause of death. In combined series with 'curative' simple cholecystectomy for gallbladder cancer, 95 of 110 patients (86%) with early tumor relapse died with or because of local recurrence, and 11 of 25 patients (48%) alive at 5 years had local recurrence. Of 16 patients with radical 'curative' cholecystectomy, 12 (75%) died with or because of local recurrence.

Kopelson et al. [39] analyzed overall patterns of failure after curative resection in an MGH series of 28 patients with gallbladder and ductal lesions. Of the 25 postoperative survivors, local-regional recurrence was the major mode of failure, occurring in 13 patients (52%). Initial spread through the wall of the organ seemed to be the best predictor of this, with local-regional recurrence occurring in 4 of 11 patients (36%) with lesions confined to the wall and 9 of 14 (64%) with lesions extending beyond the wall. The impact of adjuvant treatment on survival or local-regional control is difficult to discern in view of a paucity of published data.

Patterns of Failure – Unresected Disease

In retrospective analyses, external irradiation and chemotherapy is associated with an apparent doubling of median survival when compared with bypass alone [40]. Local control is infrequent in view of dose-limiting adjacent structures. The impact of specialized boosts with transcatheter irradiation or intraoperative electrons is difficult to discern with regard to either local-regional control or survival [40]: evaluation of local-regional control utilizing serial radiographs is difficult since the specialized boosts can produce ductal narrowing – as can tumor persistence or relapse. The impact of nodal irradiation on regional disease control is impossible to discern in view of inadequate imaging techniques and a low incidence of autopsy or reoperation in most series.

Irradiation Field Design

The tumor bed or unresected tumor should be included as well as areas of potential microscopic node involvement along the porta hepatis, pancreaticoduodenal system and celiac axis. An intravenous pyelogram can be performed at the start of treatment to be certain of left renal function, because one-half to two-thirds of the right kidney is usually within the AP:PA field. Contrast is injected into the transhepatic catheter to define ductal tumor extent, and location of pancreaticoduodenal nodes is determined with contrast in the stomach and duodenum (nodes lie adjacent to medial wall).

The initial large field volume can be treated to 40–45 Gy in 1.8-Gy fractions, 5 days/week, via a three- to four-field plan (AP and laterals or AP:PA and laterals) using blocks when possible to exclude normal stomach, small intestine, kidney, and liver [38, 40]. Use of lateral fields for part of the treatment allows decreased dose to the spinal cord, right kidney, and portions of the liver. Liver tolerance may necessitate an initial field reduction after 30–35 Gy and a second reduction after 45–50 Gy if gross disease exists. If specialized boosts are planned, the tumor/nodal dose is carried to 45–50 Gy and an additional 15–20 Gy is delivered to the primary lesion with the specialized techniques.

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Lower Gastrointestinal Cancers: Rationale, Results, and Techniques of Treatment

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This chapter discusses indications for and results of lymphatic treatment for lower gastrointestinal (GI) malignancies (large bowel and anus). As with upper GI sites, no randomized trials have been performed to test the inclusion of nodes in irradiation fields. The rationale for including nodes will be based on patterns of relapse in autopsy, reoperation, and clinical analyses.

Involvement of nodes is usually demonstrated by computed tomography (CT) evidence of nodal enlargement at both initial workup and subsequent follow-up. Although a lymphangiogram can demonstrate filling defects in normal-sized nodes, this technique is rarely utilized as a diagnostic tool for large bowel or anal cancers. Transluminal ultrasound is used diagnostically in rectal cancers. With either CT or transluminal ultrasound, the accuracy of predicting nodal involvement is $\leq 50\%$. The only procedure with accuracy $\geq 90\%$ is surgical exploration with resection or biopsy. Autopsy and reoperative series provide the best data concerning nodal patterns of failure after initial treatment.

Large Bowel

Anatomy and Tumor Spread

Lymphatic and venous drainage of lesions limited to the rectum depends on the level of the lesion. The upper rectum drains into the inferior mesenteric system via the superior hemorrhoidal vessels, and the middle and lower rectum

can, in addition, drain directly to internal iliac and presacral nodes. Lesions that extend to the anal canal can spread to inguinal nodes, and lesions that extend beyond the rectal wall spread through the lymphatic system of the invaded tissue or organ.

For left colon lesions, the inferior mesenteric system provides lymphatic and venous drainage, and the superior mesenteric system serves the right colon unless adjacent organs or structures are involved. If lesions in the sigmoid, cecal, proximal ascending, or distal descending colon involve organs or structures in the true or false pelvis, the iliac nodes may be at risk. When extrapelvic lesions involve the posterior abdominal wall, direct spread to periaortic lymph nodes can occur. If the anterior abdominal wall is involved at or below the level of the umbilicus, inguinal nodes are also at risk.

Colorectal cancers can spread by the four standard mechanisms of direct extension, lymphatic spread, hematogenous spread, and surgical implantation, but peritoneal spread is also possible. Extension within the bowel wall is rare and usually only involves short distances. Lymph node involvement is found in about 50% of patients and is usually orderly and predictable. Skip metastasis or abnormal spread occurs in only 1–3% of these patients and is felt to be related to lymphatic blockage. The major spread through lymphatic channels is cephalad, except for lesions ≤ 8 cm above the anal verge where both lateral and distal flow can occur; in female patients this could place the posterior vaginal wall at risk.

Incidence of Local-Regional Failure (LF-RF) – Surgery alone

Rectal. The risk of local-regional recurrence (tumor bed or nodal) after complete surgical resection relates to the degree of disease extension beyond the rectal wall as well as to nodal involvement [1–4] (table 1). The incidence for lesions with involved nodes but with tumor confined to the wall (modified Astler Coller C_1 or TNM T_{1-2}, N_{1-2}) varies from 20 to 40%, which is approximately the same as in the group without nodal involvement but with extension beyond the wall (MAC B_{2-3}; T_{3-4}, N_0): the risk is 20–35%. Lesions that have both nodal involvement and extension beyond the wall (MAC C_{2-3}, T_{3-4}, N_{1-2}), have nearly an additive risk, varying from 40 to 65% in clinical series to 70% in a reoperative series [1]. Tumor bed versus nodal failures could be identified in the University of Minnesota operative series in which 52 of 75 patients at risk developed relapse (tumor bed, 33 patients; perineum, 12; nodal, 20; wound implant, 4). This distinction is difficult to identify in clinical analyses, however. Therefore, the term pelvic recurrence is commonly used to include both tumor bed and pelvic nodal relapses. In a Massachusetts General Hospital (MGH) series, the incidence of both total and pelvic relapse in the 'node-negative' group increased with each degree of extension beyond the wall [2]. In patients

Table 1. Cancer of the rectum: survival and risk of LF-RF by stage with surgery alone (combined series)

TNM stage	Modified Astler Coller stage	Incidence %	Survival %	Incidence of LF-RF %
$T_{is}N_0M_0$	A	1–10	90–100	0–17
$T_{1-2}N_0M_0$	B_1	10–20	75–90	0–22
$T_{3,4a}N_0M_0$	B_2	25–45	40–70	15–30
$T_{4b}N_0M_0$	B_3			30–50
$T_{1-2}N_{1-2}$	C_1	5–15	40–70	20–40
$T_{3-4a}N_{1-2}$	C_2	30–45	15–30	30–60
$T_{4b}N_{1-2}$	C_3			50–70

with nodal involvement, the degree of extrarectal extension also appears to be an independent factor influencing the risk of local recurrence.

Colon. Data from clinical, autopsy, and reoperation series show that there is a high risk of local-regional recurrence in selected sites and stages of colon as well as rectal cancer after curative resection. In an autopsy series from MGH [5], with lesions proximal to the sigmoid, nodal failures were found in 49% of those who relapsed (tumor bed failures were not discussed). In a University of Washington clinical series, of 64 patients with a reoperation, retroperitoneal node failure was found in 34% and tumor bed recurrence in 48%. In an autopsy series of 92 patients from the same institution [6], 53 had evidence of relapse (20 of 53 or 38% had a tumor bed component of relapse, 34 of 53 or 64% had nodal relapse).

The most complete data on incidence and patterns of local-regional recurrence are contained in a University of Minnesota reoperative series [7] and a clinical analysis from MGH [8]. In the latter series of 533 patients with colon lesions, both 5-year survival and incidence of local failure were closely related to modified Astler Coller stage, with B_3, C_2, and C_3 lesions having a risk of $\geq 30\%$ (table 2). Of the 102 patients with local failure, operative pathologic confirmation was obtained in 80 patients or 79%. In this series, however, only 125 patients had either a reoperation or autopsy (23% of 533 patients at risk) and additional 'silent' tumor bed or nodal failures could have been present in some of the unexplored patients.

A total of 230 patients had reoperative procedures following curative resection of colorectal cancer at the University of Minnesota, and patterns of failure in the 165 with extrapelvic colon or with rectal lesions are compared in table 3. Since this was a select high-risk group with a majority of patients having

Table 2. Cancer of the colon: survival and patterns of failure by stage with surgery alone (MGH) [modified from 8]

Modified Astler Coller stage	At risk n	Survival %	Failure patterns (any component)[1]							
			tumor bed		nodal		liver		peritoneal	
			n	%	n	%	n	%	n	%
A	29	90	1	3	0	–	0	–	1	3
B_1	89	75	2	2	0	–	6	7	0	–
B_2	163	70	18	11	0	–	20	12	6	4
B_3	83	64	25	30	5	6	15	18	3	4
C_1	20	63	0	–	1	5	3	15	0	–
C_2	100	45	32	32	5	5	29	29	16	16
C_3	49	38	24	49	7	14	15	31	7	14
Total	533	63	102	19	21	4	88	17	33	6

[1] Represent total patterns of relapse, not initial relapse.

nodal involvement alone or in combination with extension beyond the bowel wall at the time of the initial operative procedure, data in this series cannot be compared directly with other series. LF-RF was most common with rectal lesions, but was not uncommon with primaries at other bowel sites. The highest incidence of LF-RF was within the surrounding organs and tissues loosely defined as the tumor bed (52% of failure group and 33% of total group at risk) but nodal failures were also very common (41% of failure group and 26% of total group).

Impact of Adjuvant Treatment on Survival and LF-RF

Rectal. Both pre- and postoperative adjuvant irradiation (in doses equivalent to ≥ 39.6 Gy in 1.8-Gy fractions) have resulted in a statistically significant reduction in local-regional recurrence when compared with surgery alone in randomized trials [9–16] (table 4). However, only combined modality postoperative irradiation plus chemotherapy has produced a statistically significant improvement in survival and distant metastases [13–16] (tables 4, 5). In the randomized trials, no distinction has been made between tumor bed and nodal failures; the impact of nodal irradiation on either disease control or survival is impossible to discern. Little interest exists in randomizing the extent of irradiation fields, since pelvic irradiation is well tolerated alone or in conjunction with chemotherapy.

Table 3. Cancer of the large bowel: patterns of failure by site in 165 patients with high-risk primary lesions[1] (The University of Minnesota reoperation series) [modified from 1, 7]

Sites of failure	Primary lesions											
	rectum (n = 74)		cecum (n = 37)		ascending (n = 17)		flexures (n = 13)		transverse (n = 8)		descending (n = 16)	
	n	%	n	%	n	%	n	%	n	%	n	%
Local-regional	48	65	18	49	5	29	9	69	3	38	9	56
Tumor bed	33	45	12	32	3	18	6	46	2	25	7	44
Nodal	20	27	10	27	4	24	6	46	0	–	4	25
Anastomosis (perineal)	12	16	1	3	2	12	0	–	1	13	0	–
Abdominal wound implant	4	5	1	3	0	–	1	8	0	–	1	6
Hematogenous (initial)	26	35	11	30	4	24	4	31	2	25	6	38
Liver	17	23	10	27	4	24	3	23	2	25	4	25
Lung	12	16	0	–	2	12	1	8	0	–	1	6
Peritoneal	3	4	6	16	3	18	5	38	1	13	5	31

n = Number at risk; % are of total at risk.

[1] Sixty-one of 74 rectal and 64 of 91 colon patients had involved nodes (and extension beyond wall) at time of primary resection.

Colon. In a single institution analysis from MGH [17] (table 6), the addition of postoperative irradiation and 5-FU has appeared to decrease local recurrence and improve survival in a group of patients at high risk for local recurrence after curative resection (MAC B_3, C_3, and selected C_2 and B_2; TNM T_{4b} N_{0-2}, T_3 or T_{4a} N_{0-2}). An intergroup randomized study is currently underway in which patients are randomized to 5-FU and levamisole and tumor bed nodal irradiation after curative resection (MAC B_3, C_3 and selected C_2).

Design of Irradiation Fields

Rectum and Colon. For both rectal and colon lesions, the intent is to include the primary tumor or tumor bed with 3- to 5-cm margins as well as nodal areas that either are not removed by the surgeon or cannot be removed without manipulation [3]. In most institutions, internal iliac and presacral nodes are not standardly dissected during surgery for rectal cancer because of increased morbidity and limited gain in disease control or survival; therefore, these nodes should be included in the initial irradiation volume. External iliac

Table 4. Pre- versus postoperative irradiation for cancer of the rectum: impact on disease control [modified from 4]

Sequence of XRT/OP	Incidence local recurrence, %					Incidence distant metastasis, %				
	Op	CT	XRT	XRT/CT	p	Op	CT	XRT	XRT/CT	p
Preop (5-year actuarial)										
EORTC										
Total	35	–	20	–	0.02	–	–	–	–	–
Curative	30	–	15	–	0.003	25	–	25	–	0.87
Rotterdam										
T_2	18	–	0	–	NS	26	–	45	–	NS
T_3, T_4	36	–	14	–	0.08	45	–	32	–	NS
Postop (initial failure, crude incidence)										
GTSG 7175	24	27	20	11	0.08[a]	34	27[b]	30	26[b]	–
NCCTG/Mayo 794751	–	–	25	13.5	0.04	–	–	46	29	0.01[c]
NSABP R-01										
Published	25	21	16	–	0.06	26	24	31	–	NS
Consensus conf.	30	–	19	–	0.03					
GTSG 7180	–	–	–	17 vs. 16	NS	–	–	–	26 vs. 40	0.05[d]
NCCTG 864751	–	–	–	8 vs. 12	NS[e]	–	–	–	31 vs. 40	0.03[e]
Preop vs. postop (crude incidence, local recurrence; 5-year actuarial distant metastasis)										
Swedish Trial	–	–	12 vs. 21	–	0.02	–	–	28 vs. 37	–	0.30

XRT = External irradiation; Op = operation; CT = chemotherapy; NS = not statistically significant; DM = distant metastases; CI 5-FU = continuous infusion 5-fluorouracil.

[a] XRT vs. no XRT.

[b] GTSG advantage to chemotherapy vs. no chemotherapy at 20 vs. 30% (DM only), 27 vs. 32% (any DM).

[c] Mayo 5-year actuarial distant metastases (DM) rate of 33 vs. 52%, XRT CT vs. XRT.

[d] Advantage XRT 5-FU vs. XRT 5-FU Me CCNU.

[e] Advantage to XRT CI 5-FU vs. XRT bolus 5-FU.

nodes are not a primary nodal drainage site and should be included only when pelvic organs with major external iliac drainage are involved by direct extension (i.e., sigmoid lesion with bladder involvement; rectal cancer with involvement of bladder, prostate, cervix, or vagina).

The inferior mesenteric system is, in our opinion, the surgeon's domain for left colon lesions, as essentially four levels of nodes can be removed without manipulation. Many surgeons sacrifice the inferior mesenteric artery just below the left colic branch, which leaves only 1–3 cm of vessel and potential nodes. For right colon lesions, removal of the superior mesenteric system is adequate but less inclusive than the inferior mesenteric resection because of the need to

Table 5. Pre- versus postoperative irradiation for cancer of the rectum: impact on survival[1] [modified from 4]

Sequence of XRT/Op	Advantage seen	Disease-free, % (p value)	Overall, % (p value)
Preop (all stages)			
EORTC			
Curative	preop XRT vs. Op alone	not given	69 vs. 59 (0.08)
Total	none	56 vs. 51 (0.54)	52 vs. 49 (0.69)
Rotterdam			
T_3, T_4	preop XRT vs. Op alone	not given	50 vs. 18 (0.001)
T_2	none	not given	62 vs. 70 (NS)
Postop[2] (5-year actuarial data and two-tail p values unless specified			
GTSG 7175	XRT CT vs. Op	70 vs. 46 (0.009)	58 vs. 45 (0.005, one-tail)
	XRT CT vs. XRT	70 vs. 52 (0.06)	58 vs. 52 (not given)
NCCTG/Mayo 794751	XRT CT vs. XRT	59 vs. 37 (0.002)	58 vs. 48 (0.025)[3]
NSABP R-01	CT vs. Op	41 vs. 30 (0.006)	53 vs. 43 (0.05)
GTSG 7180 (3-year data)	XRT 5-FU ± MeCCNU	68 vs. 54 (0.20)	75 vs. 66 (0.58)
NCCTG 864751 (4-year data)	XRT CI 5-FU vs. XRT bolus 5-FU	63 vs. 53 (0.01)	70 vs. 60 (0.02)
Preop vs. postop (all stages)			
Swedish	preop vs. postop	not given for total group	43 vs. 37 (0.43)

For abbreviations, see table 4.

[1] All data is from controlled multi-institution randomized trials.

[2] Postop-MAC stages B_2, B_3, C_1, C_2, C_3 (TNM stage II, III, or $T_{3-4}NO$, T_{is-4} N+).

[3] Mayo 5-year overall SR 70 vs. 57% postop XRT CT vs. XRT (p 0.01).

spare the ileocolic branches to the small bowel. For extrapelvic colon lesions, unresected nodal areas are included in irradiation portals only if nodes along the main mesenteric vessels or near the surgeon's mesenteric ligature are histologically positive or the lesion is adherent to structures that place a nodal area at risk, because the nodal portion of the field includes much additional small bowel.

The dose to the extended tumor bed/nodal portal should be 45–50 Gy in 1.8-Gy fractions over 5–6 weeks (usually two or more fields per day, 5 days/week). Strong consideration should be given to the use of a boost field portal to the primary tumor bed, and possibly the immediately adjacent nodes, if the large field dose is in the 45-Gy range. Our usual total dose in the boost field with both preoperative and postoperative irradiation of rectal cancer is 50–55 Gy in 6–6.5 weeks.

Table 6. Colon cancer: stage versus 5-year actuarial local control and survival with surgery and adjuvant irradiation and 5-FU (MGH)

MAC stage	Surgery[1]				Surgery plus irradiation and 5-FU[2]		
	pts n	local control %	survival, %		pts n	local control %	disease-free survival %
			disease-free	overall			
B_2	163	90	78	70	23	91	72
B_3	83	69	64	63	53	93	78
C_2	100	64	48	44	54	69	48
C_3	49	47	38	37	39	72	53

[1] From Willett et al. [8].
[2] From O'Connell et al. [16].

Rectum. Most tumor bed failures are in the posterior one-half to two-thirds of the true pelvis [1, 3, 7], and the internal iliac and presacral nodes have a posterior location relative to external iliac nodes. Lateral treatment fields can logically be combined with anterior-posterior (AP:PA) fields to reduce the dose to anteriorly located normal structures, including small bowel. Field arrangements (fig. 1) depend on the location of the primary tumor, presence or absence of adjacent organ involvement, and area and number of nodes involved [3].

Colon. The target volume should include the tumor bed as well as areas of potential or proven nodal involvement. Whenever feasible, the initial margin beyond tumor bed should be 5 cm (minimum 3 cm; tumor bed is defined as the affected segment of the large bowel, and when present, the adjacent organ or structure to which it was adherent or invading). Node groups are included routinely if nodes were involved at the level of the proximal surgical vascular ligature or an area of tumor adherence places a group of nodes at risk (para-aortic nodes with adherence to posterior abdominal wall (fig. 2a); external iliac with adherence to iliac fossa or pelvic side wall) (fig. 2b). When tumor adherence places node groups at risk, the acceptable superior-inferior extent of nodal coverage is the same as tumor bed plus margin.

Multiple field techniques are useful with primary lesions of the sigmoid colon (fig. 3), but for such lesions in other parts of the colon parallel opposed AP:PA fields are used for the major portion of treatment unless CT studies or

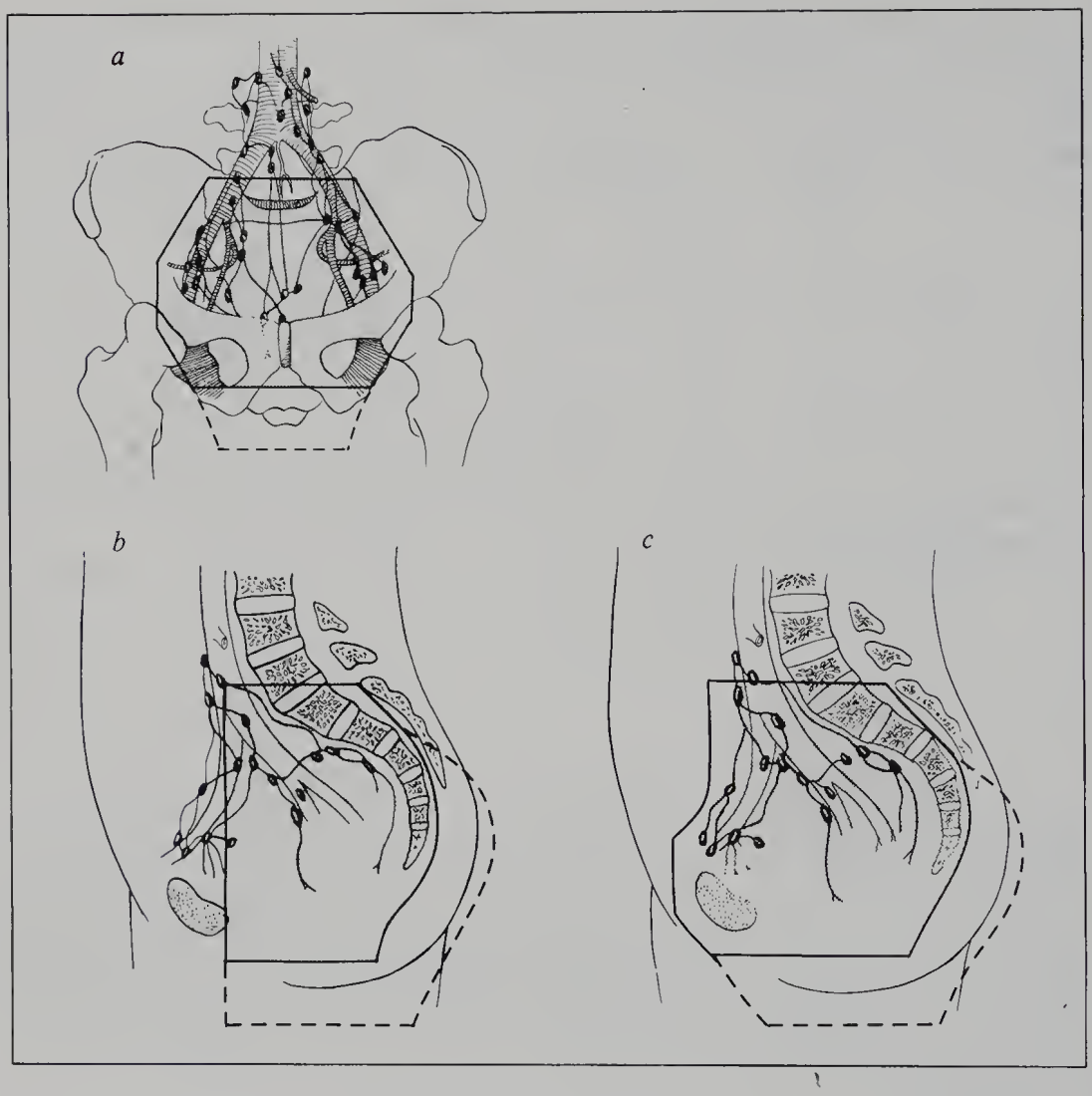

Fig. 1. Idealized irradiation fields for rectal cancer either preceding or following anterior resection or following abdominoperineal resection (APR); interrupted lines indicate alterations of fields after APR. *a* AP:PA field. *b* Lateral field when only internal iliac and presacral nodes are at risk. *c* Lateral field when external iliac nodes are also at risk [from 26, with permission].

clip placement suggests that multifield techniques can spare normal tissues. An excretory urogram should be done at or before the start of treatment to define renal function if more than one-third of one kidney may be in the field, because at least two-thirds of one kidney needs to be excluded from the high-dose fields. For extrapelvic right or left colon locations, the patient should be in a decubitus position for a portion of treatment if small bowel films reveal a good shift of small intestine and this position can be reproduced reliably.

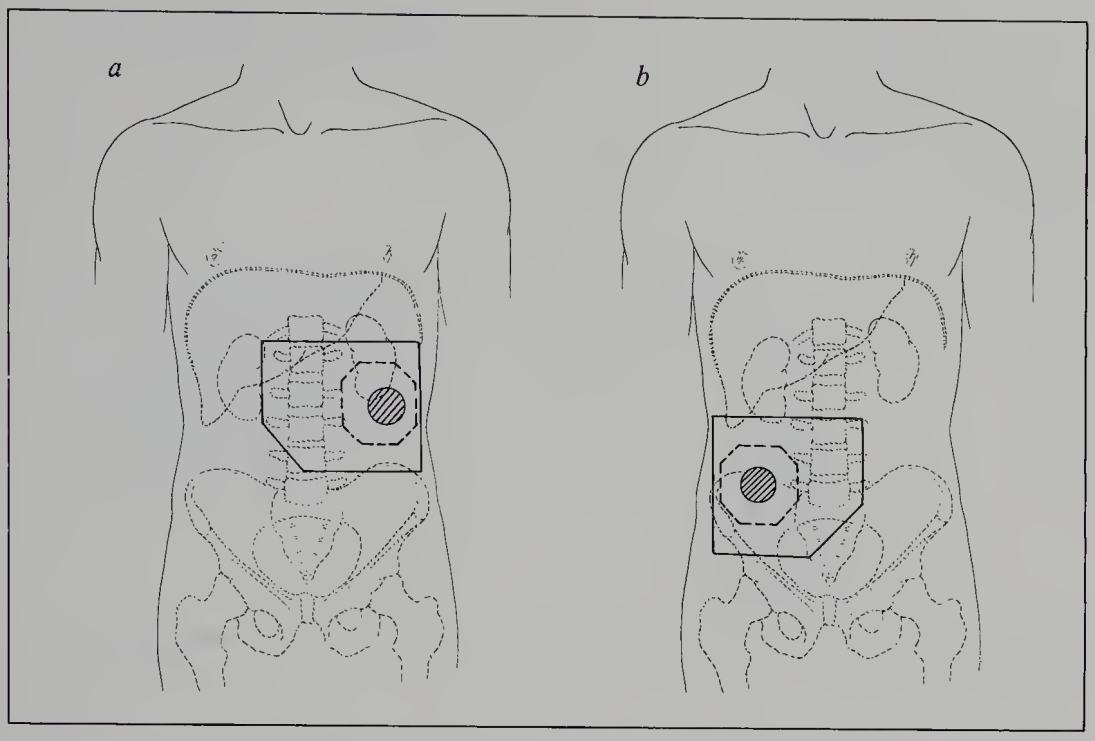

Fig. 2. Idealized postoperative AP:PA irradiation fields for extrapelvic colon cancer (tumor bed and nodal regions). *a* Para-aortic node are at risk in addition to tumor bed due to tumor adherence to posterior abdominal wall with descending colon cancer. *b* External and common iliac nodes are at risk in addition to tumor bed from proximal ascending colon cancer.

Anus

Anatomy and Pathways of Spread

For evaluation of both tumor spread and ultimate prognosis, these lesions are commonly divided into those of the anal canal versus the perineal aspect of the anus (also known as external margin or tumors below the mucocutaneous junction). Anal canal lesions more frequently exhibit local invasion of adjacent perianal tissues and can also involve the sphincter muscles or adjacent organs.

Lymphatics of the anal canal drain either to the superficial inguinal nodes or to nodes of the low rectum (internal iliac and inferior mesenteric). Lesions on the external margin drain primarily to the superficial inguinal nodes. Perirectal or inferior mesenteric node involvement at the time of initial resection has varied from 28 to 64% and inguinal node involvement from 13 to 25%. In a Mayo Clinic analysis by Boman et al. [18], the incidence of nodal involvement at diagnosis was $\geq 30\%$ with lesion size > 2 cm independent of histology, and with grade 3 or 4 nonkeratinizing basaloid tumors of any size.

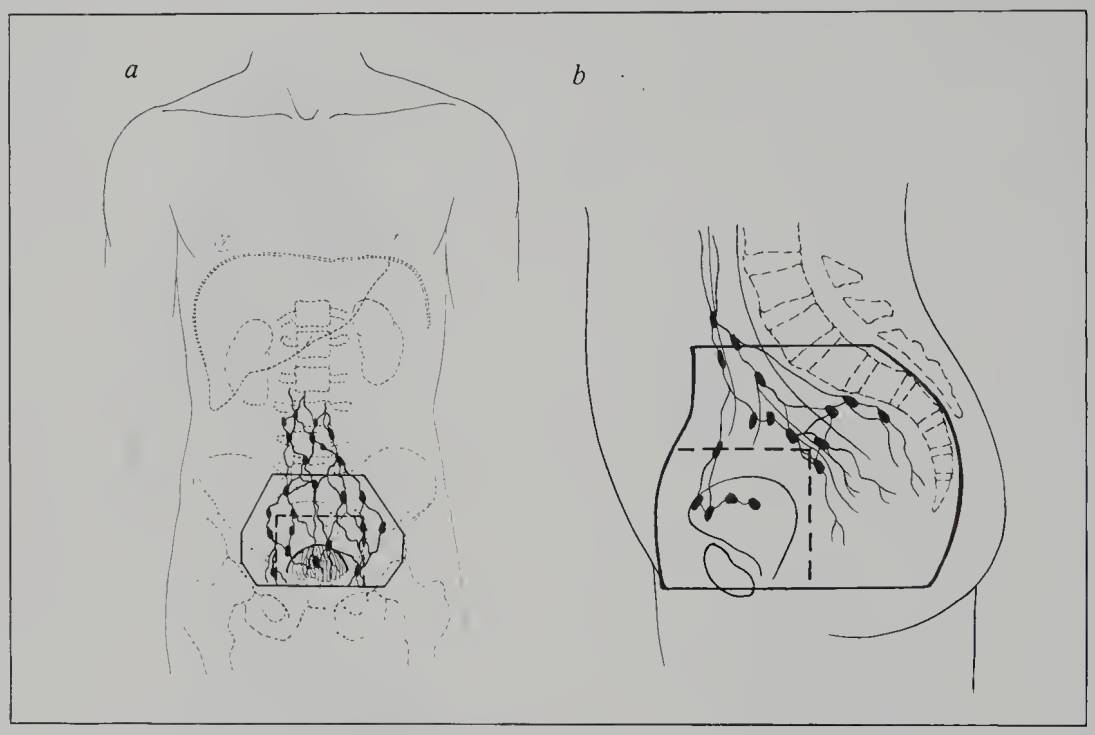

Fig. 3. Idealized multiple field irradiation technique following resection of a sigmoid colon cancer that was adherent to the bladder (large field – solid lines; boost field – interrupted lines). *a* AP:PA. *b* Paired laterals.

LF-RF – Surgery Alone

Although abdominoperineal resection has been replaced with irradiation and chemotherapy as the standard of care for anal cancer, some excellent data exist on failure patterns after surgery alone. In the Boman analysis [18], LF-RF was shown to be the predominant relapse pattern in 106 evaluable patients with abdominoperineal resection (table 7). Of the 38 evaluable patients who relapsed, 84% had a local-regional component of failure, and 29% had a distant component. The risk of local relapse was related to degree of local invasion and nodal involvement. Fifteen of 38 (39%) had an inguinal node component of relapse. Seven patients had inguinal node dissection for clinically apparent involvement at the time of abdominoperineal resection. The 5-year relapse-free survival was 71% (5 of 7).

LF-RF – Radiation and Chemotherapy

Organ preservation has become standard treatment for most anal cancers, but questions still exist with regard to treatment optimization. Both irradiation and local excision [19, 20] and irradiation plus chemotherapy [21, 23] have resulted in excellent local control and survival, leaving some to ponder whether we can improve upon current standard treatment.

Table 7. Cancer of the anus: stage versus survival and patterns of failure after abdominoperineal resection (Mayo) [modified from 18]

Mayo stage		Incidence %	5-year SR (n = 114)		Patterns of initial failure (component)			
					local		distant	
			n	%	n	%	n	%
A	Mucosa and submucosa	4	4/4	100	0	–	0	–
B_1	Internal sphincter	24	20/26	77	2	8	2	8
B_2	External sphincter	13	10/13	77	3	23	0	–
B_3	Beyond sphincters	29	15/31	48	14	48	2	7
C	Nodes involved	36	19/40	48	13	36	7	19

Table 8. Cancer of the anus: survival and patterns of failure with irradiation and chemotherapy (PMH) [modified from 22]

Treatment	Component of failure (at any time)								5-year survival, % (cause-specific)	
	primary		nodal		distant		total			
	n	%	n	%	n	%	n	%		
Continuous XRT										
XRT	25	44	11	19	10	18	28/57	49	68	
XRT, 5-FU, Mito	2	13	0	–	1	6	3/16	19		p 0.14
Split-course XRT									76	
XRT, 5-FU, Mito	8[1]	15	5[1]	9	11	21	17/53	32		p 0.02
XRT, 5-FU	26	40	5	8	8	12	31/65	48	64	

XRT = External irradiation; 5-FU = 5-fluorouracil; Mito = mitomycin.
[1] 11/53 or 21% had pelvic failure (primary or nodal).

Separate analyses by Princess Margaret Hospital (PMH) [22], University of Kansas [24], and RTOG investigators [21] support the need to evaluate both irradiation dose levels as well as type and duration of chemotherapy in an attempt to improve both local control and systemic control of disease (table 8). The pelvic failure rate (anal primary and pelvic and inguinal nodes) in those series range from 20 to 30% at dose levels of approximately 40–50 Gy plus chemotherapy (1.8- to 2.0-Gy fractions in the US analyses and 2.0–2.5 Gy in

the PMH trial). In the PMH analysis, the most optimal combination of irradiation plus 5-FU-MMC still resulted in a 19% pelvic failure rate (13 of 69) and 17% systemic failure rate (12 of 69) (table 8). A nodal component of failure was found in 5 (7%) which may be falsely low since intrapelvic node relapse is difficult to diagnose without reoperation or autopsy. In RTOG trial 83-14 in which irradiation to 40.8 Gy was combined with 5-FU-MMC, the 3-year colostomy-free survival is 63% [21]. Pelvic failure has occurred in 24/77 patients or 31% (5-year actuarial rate of 32%) and systemic failure in 12/77 patients or 16% (5-year actuarial rate of 19%).

Primary tumor control may increase as a function of irradiation dose level. In pooled data on 57 patients from five Kansas City institutions, 77% of patients received chemotherapy with irradiation – 5-FU with MMC or CDDP [24]. Local control (LC) was achieved in 81%; all local failures occurred within 1.5 years of treatment and salvage was achieved in 8 of 11 for an eventual LC of 95%. LC by irradiation dose level was as follows: ≤ 45 Gy, 64%; 45–55 Gy, 72%, and > 55 Gy, 92% ($p = 0.05$). On the basis of Cox multivariate analysis, RT dose > 55 Gy was the only variable associated with improved LC.

Irradiation field design has been shown to have a probable impact on nodal control. In early trials by Papillon et al. [25], no attempt was made to include pelvic nodes and the incidence of documented nodal failure was 24%. This was reduced to 3.6% after fields were appropriately altered to include pelvic nodes. Elective inguinal irradiation appears to decrease the risk of subsequent inguinal failure (risk of 11–24% without irradiation versus 0–5% with irradiation). In a PMH analysis by Cummings et al. [22], the risk was 18 versus 3% and in Papillon's series [25] 13 versus 0%.

Radiation Field Design

Currently most single institution and group studies design fields to include the primary lesion as well as major nodal groups (inguinal and pelvic) to 30–36 Gy in 1.8- to 2.0-Gy fractions when irradiation is combined with concomitant chemotherapy or 45 Gy in 25 fractions for irradiation alone schemas. A majority of investigators utilize parallel-opposed fields to those dose levels, with the superior field extent varying by series from the level of the sacral promontory to the bottom of the sacroiliac joint (fig. 4). If the superior field extent is at the sacral promontory level and a nodal dose of 45 Gy is planned, lateral fields could be considered for a component of treatment in order to reduce dose to the small bowel. When the superior field extent is at the bottom of the sacroiliac joint, lateral fields would be of little value except for boost fields to the primary lesion.

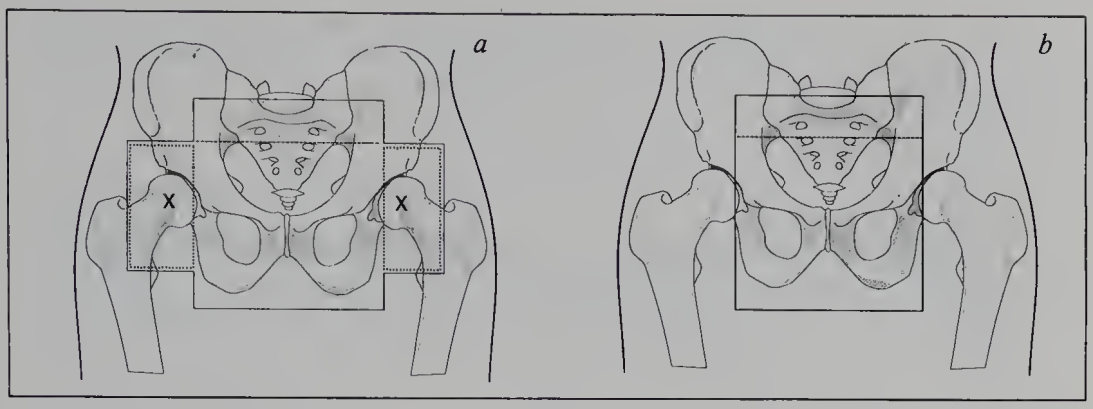

Fig. 4. Idealized AP:PA irradiation fields for primary anal cancer. *a* Anteroposterior field includes primary tumor plus pelvic and inguinal nodes. Lateral inguinal nodes are brought to prescribed dose with the aid of electron boost fields (interrupted lines). *b* Posteroanterior field includes primary tumor plus pelvic nodes and medial inguinal nodes.

Lymphangiograms can be useful in designing the nodal portion of shaped blocks for both AP:PA and lateral fields. In order to decrease dose to the head and neck of the femur, inguinal nodes can be excluded from the PA field and an anterior electron boost can be used to supplement the dose given to those nodes with the anterior photon field. In patients with uninvolved nodes who are treated with irradiation plus 5-FU-MMC, the nodal groups are excluded after a dose of 30–36 Gy. The primary lesion plus a 2- to 2.5-cm margin is then carried to a higher dose with multiple field techniques including lateral fields.

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Renal, Renal Pelvis and Ureteral Tumors: Should Retroperitoneal Nodes Be Treated?

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Renal tumors are relatively rare, accounting for approximately 3% of adult malignancies. Eighty-five percent are renal cell carcinomas which arise in the proximal renal tubules. Eight percent are transitional cell carcinomas which originate in the epithelium lining the intrarenal collecting system, renal pelvis and proximal ureter. These two malignancies have different origins and natural history and, therefore, will be discussed separately.

Renal Cell Carcinoma

Renal cell carcinoma is the third most common urologic cancer after prostate and bladder. It is estimated that in 1992, 26,000 new cases of and 10,700 deaths from renal cell carcinoma will be reported [1]. Its peak incidence is in the sixth and seventh decades of life and the male:female ratio is 1.5:1.

Surgical resection is the only known curative therapy for renal cell carcinoma. Five-year disease-free survival rates vary from 0 to 75% depending on the stage of the disease and, probably, on the extent of resection. Since the classical article of Robson [2] in 1963 showing that a more aggressive surgical operation is associated with better survival and because of the unavailability of good adjuvant therapy, radical nephrectomy has now become the preferred operation. In contrast to simple nephrectomy where only the kidney with its perinephric fat is excised, radical nephrectomy involves removal of the kidney, perinephric fat, Gerota's fascia, ipsilateral adrenal gland and the regional lymph nodes. Is this enthusiasm for more radical resection justified? Let us first examine the mode of spread of renal cell carcinoma and what has been reported in the literature.

Table 1. Renal cell carcinoma: stage at initial presentation, n (%)

Stage	Skinner et al. [9]	Peters and Brown [6]	Stanford
I	102 (33)	108 (30)	47 (33)
II	22 (7)	69 (19)	43 (30)
III	108 (35)	31 (9)	29 (20)
IV	77 (25)	148 (42)	24 (17)
Total	309	356	143

Staging

The staging system is based on the pathologic findings at nephrectomy and on the presence or absence of metastatic disease at diagnosis. The system most commonly used was first proposed by Flocks and Kadesky [3] and later modified by Robson and co-workers [2, 4]. It is as follows:

- *Stage I:* Tumor confined to the kidney.
- *Stage II:* Tumor involves the perinephric fat but still confined to within Gerota's fascia.
- *Stage III:* Tumor involves the regional lymph nodes or renal vein with or without extension into the vena cava, or beyond Gerota's fascia.
- *Stage IV:* Invasion of contiguous structures or evidence of distant metastasis.

The number and percentage of patients in each stage is shown in table 1, which covers three different series. The Stanford series is the most recent. With the increasing use of ultrasound to evaluate abdominal disease, more renal tumors are discovered before they cause symptoms and, probably, at a less advanced stage. Although the percentage of patients in stage I is the same in the three different series, the Stanford series has less patients in the more advanced stages probably because of earlier diagnosis. Actually, between 1983 and 1992, 38 of the 143 patients in the Stanford series were discovered incidentally and of these 31 were stage I.

Table 2 shows the sites and frequency of local spread in three different series. Regional lymph node metastasis varies between 14 and 27%. The most commonly involved nodes are the renal hilar, and the ipsilateral lumbar nodes – paracaval in right-sided tumors and para-aortic in left-sided tumors (table 3).

Treatment

In 1963, Robson [2] showed that a more radical resection is associated with better survival. He compared two different series: an earlier series of 19 patients

Table 2. Renal cell carcinoma: sites of lymphatic spread

	Hulten et al. [7]	Stanford
Total number of patients	22	143
Number with lymph node metastases	7 (27%)	20 (14%)
Renal hilum	–	19
Ipsilateral lumbar	4	8
Contralateral lumbar	1	–
Iliac	2	2
Interaortocaval	–	1
Mediastinal	1	–
Supraclavicular	2	–

Table 3a. Renal cell carcinoma: sites and frequency of local spread, %

	Hulten et al. [7]	Angervall et al. [8]	Stanford
Regional lymph nodes	27	22	14
Perinephric fat	–	22	30
Adrenal	–	10	9

Table 3b. Renal cell carcinoma: lymph node metastasis and survival

Primary stage	Incidence of lymph node metastasis, %	Survival with negative lymph nodes, %	Survival with positive lymph nodes, %
T1	12	80	30
T2	13	75	25
T3	35	35	15
T4	60	5	<5

treated by simple nephrectomy with a 5-year survival rate of 33%, and a later series of 51 patients treated by radical nephrectomy with a 5-year survival rate of 66%. Since then, radical nephrectomy has become the treatment of choice for patients with localized or locoregional renal cell carcinoma.

There are many reports comparing the results of simple and radical nephrectomy. In 1978, Patel and Lavengood [5] reported on 85 patients treated by simple nephrectomy with a 5-year survival rate of 32%, and on 44 patients treated by radical nephrectomy with a 5-year survival rate of 67%. In 1980,

Peters and Brown [6] showed that in the less advanced stages I and II, lymph node dissection did not improve survival; however, in the more advanced stages III and IV, lymph node dissection was associated with improved survival.

Phillips and Messing [10] recently reported on the role of lymphadenectomy with nephrectomy. Of 7 patients with positive nodes who were treated with nephrectomy without lymphadenectomy, 6 recurred locally compared to only 1 local recurrence in 6 patients with positive nodes treated with nephrectomy and lymphadenectomy. Of 15 patients with clinically negative nodes who did not undergo lymphadenectomy, 8 recurred locally compared with only 1 of 27 patients with pathologically negative nodes who underwent nephrectomy with lymphadenectomy. They concluded that lymphadenectomy was effective in achieving better local control. They also found that nodal metastasis was the only significant predictor of local recurrence. Lymphadenectomy did not prolong hospital stay or add to the morbidity of nephrectomy.

Adjuvant Therapy

Renal cell carcinoma is radioresistant and, when treated, requires high doses of irradiation. Early retrospective studies have suggested a benefit from irradiating the renal bed following nephrectomy [11]; however, randomized, prospective studies failed to confirm such a benefit [12–14].

Renal cell carcinoma is also resistant to systemic chemotherapy. Progestational compounds have also been tried in prospective randomized studies and have failed to show a survival benefit [15]. α-Interferons are now being evaluated but the results are not yet available.

Comment

Without randomized prospective studies comparing simple to radical nephrectomy, the value of a more aggressive surgical treatment can never be ascertained. However, because of the lack of adequate adjuvant therapy for renal cell carcinoma, the fact that the majority of patients have locoregional disease at presentation, and the historical comparisons favoring a more aggressive resection, radical nephrectomy has to be considered the standard therapy for patients with renal cell carcinoma. Moreover, it offers a more accurate staging and is not associated with increased morbidity or prolonged hospital stay.

Transitional Cell Carcinoma of the Renal Pelvis and Proximal Ureter

Transitional cell carcinoma of the upper urinary tract is rare, accounting for 7% of renal tumors and 1% of all urologic malignancies. It is part of a field

change disease which for, unknown reasons, affects the bladder much more frequently than the upper urinary tract. Of 350 cases of transitional cell carcinoma of the urinary tract seen at Stanford in a 5-year period, 22 (6%) originated in the upper urinary tract, 15 in the renal pelvis and 7 in the ureter. Only 3% of patients with transitional cell carcinoma of the bladder have or develop upper tract tumors while 30% of patients with upper tract transitional cell carcinoma have or develop bladder tumors. Bilaterality occurs in 3% of patients of which 0.7% are synchronous and 2.3% are asynchronous.

Hematuria is the most common presenting sign, occurring in 80% of patients. Flank pain due to ureteral obstruction and flank mass are seen in 10–20% of patients. An intravenous urogram is abnormal 95% of the time; however, it is a poor predictor of the stage of the disease. Retrograde pyelography and, more recently, ureteroscopy confirm the diagnosis. CT scans are used in almost all cases as staging procedures to evaluate the extent of local disease, the status of the lymph nodes and the presence of distant metastasis. Urinary cytology obtained by voiding or, for better accuracy, at the time of cystoscopy and ureteroscopy are very useful in predicting the grade of the tumor. Cytology is usually negative in low-grade tumors and positive in more than 85% of high-grade tumors.

Mode of Spread

Transitional cell carcinoma of the upper urinary tract spreads by direct invasion, by mucosal seeding and by vascular and lymphatic invasion. Lymph node metastasis at initial clinical staging is 7% compared to a true pathologic incidence of 18%. The incidence of lymph node metastasis varies with stage: superficial tumors rarely metastasize to lymph nodes while pT3 and pT4 tumors have a 48 and 78% incidence of lymph nodal involvement, respectively. Nineteen percent of patients will have metastatic disease at initial evaluation [16].

Staging

Because it is rare, relatively little is known about upper tract transitional cell carcinoma. Stage for stage, it behaves like bladder cancer [17] and therefore, whatever seems to apply to bladder cancer applies to upper tract transitional cell carcinoma. While accurate clinical staging of bladder tumors is possible via transurethral biopsies, both superficial and deep, it is not possible for upper tract tumors because of access limitations and the dangers of perforation and extravasation with deep biopsies. As a result, clinical staging often underestimates the extent of the disease and therefore, for more accurate staging a stage is not assigned until after pathologic examination of the surgical specimen, unless metastatic disease is present at initial clinical evaluation.

Table 4. Staging of upper tract transitional cell carcinoma

Corresponding bladder tumor stage (Jewett)	Cummings [18]	TNM	Definition
CIS	I	pTis	Carcinoma in situ
O	I	pTa	Papillary tumor confined to mucosa
A	II	pT1	Invasion of submucosa
B	III	pT2	Invasion of muscular wall
C	III	pT3	Invasion of peripelvic or periureteral fat and renal parenchyma
D	IV	pT4 N+ M+	Invasion of adjacent organs, lymph node and/or distant metastasis

Table 5. Stage and grade at initial diagnosis [modified from 19]

Stage	Grade		
	I	II	III
Ta	4	5	1
T1	–	13	5
T2	–	3	11
T3	–	–	12

There are different staging systems which are compared in table 4. Grade of tumor correlates well with the stage (table 5).

Treatment

The standard treatment of transitional cell carcinoma of the upper urinary tract is radical nephroureterectomy, excising the kidney, perinephric fat, Gerota's fascia, the entire ureter with a cuff of bladder wall around the ureteral orifice, and regional lymphadenectomy. Survival rates are excellent for low-grade, low-stage tumors and poor for high-grade, more advanced disease (tables 6, 7).

Over the past several years more conservative surgery, such as local resection rather than nephroureterectomy, is being applied to a select group of

Table 6. Upper tract transitional cell carcinoma

Primary stage	Incidence of lymph node metastasis, %	Survival with negative lymph nodes, %	Survival with positive lymph nodes, %
T1	5	90	15
T2	25	50	15
T3	48	30	10
T4	78	10	5

Table 7. Five-year survival rates (%) for upper tract transitional cell carcinoma: four different series

Stage	Batata et al. [20]	Huben et al. [19]	Das et al. [21]	Guinan et al. [22]
pTa				75
pT1	91		97	
		74		87
pT2	43		53	
pT3	23		18	54
		15		
pT4	0		5	14

patients with ureteral tumors in order to preserve renal function. Such conservative surgery is supported by the following experience: for grade 1 tumors, the 5-year survival rate was 88% after radical surgery and 75% after conservative resection. For grade 2 tumors, the 5-year survival rate was 90% after radical surgery and 46% after conservative resection [23]. Such data suggest that low-grade, low-stage solitary ureteral tumors can safely be treated with local resection. Multiple or high-grade, high-stage ureteral tumors should be treated with nephroureterectomy. Because local resection is not feasible in most renal pelvic and calyceal tumors, they should be treated with nephroureterectomy.

The role of lymphadenectomy for upper tract transitional cell carcinoma is not known. There have been no studies, retrospective or otherwise, to evaluate its efficacy. Since the survival of patients with more advanced local disease who tend to have a higher incidence of lymph node metatasis is poor, irrespective of the extent of resection, one may safely assume that lymphadenectomy does not improve survival. However, since lymphadenectomy does not add to the morbidity of radical nephrectomy and does not increase the hospital stay [10], it is recommended for better staging of the disease and for the selection of patients for adjuvant therapy.

Adjuvant Therapy

Radiation Therapy. The role of adjuvant radiation therapy for upper tract transitional cell carcinoma is controversial. Batata et al. [20] recommended postoperative irradiation with 6,000 rad to invasive and locally extensive disease. Brady et al. [24] reported that 3 of 5 patients followed for 5 years survived without evidence of disease after adjuvant radiation therapy. A recent study by Brookland and Richter [25] in 41 patients treated with postoperative irradiation showed that local recurrence was less but the rate of distant metastasis was the same. Bergman and Hotchkiss [26] recommended the use of radiation therapy only for symptomatic metastatic disease.

Chemotherapy. Cisplatin-based combination chemotherapy is effective against metastatic transitional cell carcinoma [27, 28] irrespective of origin, however its role as neoadjuvant and adjuvant treatment is still under investigation [29]. The protocol at Stanford uses a combination of cisplatin, methotrexate and vinblastine – CMV. Of 8 patients with locally advanced or metastatic transitional cell carcinoma of the upper tract treated with CMV, 2 progressed on treatment and died, 2 recurred (at 6 and 8 months, respectively) and died, and 4 are alive without disease (at 3, 3, 5 and 6 years, respectively) following treatment.

In summary: Transitional cell carcinoma of the upper urinary tract is rare. Tumors arising in the renal pelvis and calyces should be treated with nephroureterectomy, irrespective of stage and grade. Low-grade, low-stage ureteral tumors may be treated with conservative resection in order to preserve renal function. High-grade, more advanced ureteral tumors should be treated with nephroureterectomy because of the high incidence of recurrence associated with local resection. The role of lymphadenectomy for upper tract transitional cell carcinoma has never been evaluated; however, it is recommended for better staging of the disease and for recommendations regarding adjuvant therapy. Adjuvant radiation therapy to sterilize microscopic residual disease and prevent local recurrence is logical. The role of adjuvant chemotherapy is under investigation.

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Prostate Cancer: Defining the Roles of Elective and Therapeutic Nodal Irradiation

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The incidence of prostate cancer will continue to rise in the United States as the population ages and detection programs become more available. Much of the explicit (as well as implicit) decision-making in the clinical management of prostate cancer revolves around controversies related to the status of lymph nodes [1]. In 1992, over 8,000 patients with clinical stages T1/T2 and nearly 32,000 with stages T3/T4 had positive lymph nodes [2]. Thus, the problem of lymphadenopathy is not an insignificant concern for physicians caring for prostate cancer patients.

Five objectives will be pursued in this review. First, the magnitude of the problem will be defined. Second, alternatives for diagnosing and predicting nodal involvement will be explored. Third, current concepts for elective nodal irradiation (ENI) will be described. Precedent exists for the use of ENI from not only multiple cancer sites but also multiple tumor cell types [3–6]. Since it is well known that prostate cancer can systematically spread to regional nodal drainage stations [7], the principles of ENI ought to be adaptable to this disease. Fourth, therapeutic irradiation of involved nodes will be discussed. In interpreting these data, it must be stressed that most published reports neither account for PSA-based follow-up to calculate 'NED survival' nor separately analyze those patients who received hormonal manipulation in addition to local treatment. Finally, our present management program will be delineated and potential opportunities for further investigation will be proposed.

Extent of the Problem

It is desirable to determine the scope of lymph node metastases in prostate cancer in order to implement appropriate therapy and design workable clinical trials. Approximately 25% of patients with clinical stages T1, T2 disease and 40% of those with T3, T4 disease were historically reported to have positive nodes [2]. But in a recent report of 521 consecutive patients staged at Washington University School of Medicine between 1983 and 1991, Petros and Catalona [8] observed a dramatically lower incidence of nodal disease (3.3% A2, 5.3% B1, 9.7% B2) which they attributed to greater efforts in diagnosing prostate cancer at earlier stages. It remains to be seen whether other modern series will confirm these findings.

Documentation of Nodal Disease

Lymphadenectomy

Lymphadenectomy remains the most accurate method to determine nodal extension from prostate carcinoma, but over time, the procedure has been converted into a nodal sampling that falls short of a gold standard [7]. Conventional lymphadenectomy refers to removal of lymph-bearing tissue from the distal part of the common iliac, the external iliac, the main trunk of the hypogastric, and the obturator regions. In modified radical lymphadenectomy, surgeons forego dissection along the lateral external iliac and the common iliac [9, 10]. Conversely, extended lymphadenectomy adds dissection of the entire common iliac, presacral and lateral sacral areas [11]. Hanks [7] has cautioned that the current sampling may miss isolated metastases in at least 12% [12] and perhaps 33% [11] of those who are truly node-positive. Although enthusiasm has mounted for laparoscopic node dissection, this procedure is highly operator-dependent and tends to harvest fewer nodes than the more conventional surgical approaches [13]. At this time it is not clear that the ability of the laparoscope to detect positive nodes is comparable to open procedures.

Nonsurgical Determination of Lymph Node Metastases

Three imaging modalities have been employed to assess nodal metastases from prostate cancer: lymphography (LAG), computed tomography (CT) and magnetic resonance imaging (MRI).

The primary advantage of LAG is its ability to detect small filling defects in normal-sized lymph nodes (in contrast to CT and MRI which require increased nodal size to detect abnormality). The anatomic drawback to the use of LAG is its failure to reliably demonstrate the internal iliac chain or the presacral node groups.

CT can only be used to diagnose malignant lymphadenopathy on the basis of size criteria (e.g. >1.5 cm) since nodal architecture is not accurately assessed by CT scan. Although it was initially hoped that MRI would supplant the other modalities owing to its ability to depict signal changes in diseased nodes, the accuracy of MRI in diagnosing involved nodes has not eclipsed CT because even MRI only reliably evaluates lymph node size [14]. Body coil MRI had no value in a prospective trial conducted by the Radiological Diagnostic Oncology Group [15] where only 1 of 23 pathologically positive patients was identified prior to surgery.

The failure of CT and LAG to discriminate clinical outcome has been rigorously documented by Hanks et al. [16]. Those authors carried out a detailed review of two prospective trials in which lymph node status was determined by lymphography, CT, or biopsy. Only biopsy proof of nodal disease could be related to NED survival, overall survival and freedom from metastases. In summary, imaging tests cannot be relied upon to assess lymph node metastases from prostate cancer.

Radiotherapeutic Management

Radiation oncologists have been called upon to prophylax microscopic nodal involvement with ENI and to address clinically involved nodes with a variety of therapeutic strategies. The remainder of this communication will consider these respective roles.

Elective Nodal Irradiation

ENI has been reported from centers where nodal status was unknown, radiographically assessed, or pathologically documented. Given this wide range of knowledge of nodal status it is essential to review the experiences from these respective institutions separately (table 1).

ENI: Unknown Nodal Status. The first report to suggest a statistically significant benefit for ENI came from McGowan [17]. He found that patients with advanced disease (i.e., involvement of both prostatic lobes or extraprostatic extension) enjoyed improved disease-free survival at 5 years when treated through 'extended' instead of 'localized' fields (63 vs. 35%; $p = 0.01$). Unfortunately, no attempt (either by radiologists or pathologists) was made to systematically determine nodal status at the University of Alberta.

ENI: Radiographic Determination of Nodal Status. The desire to settle the controversy over the appropriate volume of disease to irradiate in prostate cancer was reflected by the ability of the RTOG to mount two large-phase III trials asking questions directed solely at this important technical issue. In

Table 1. Impact of ENI

Series	Determination of nodal status	n	Stage	Tx	Outcome (5 years) %
McGowan [17]	unknown	91	B2/C	ENI	63 DFS
		44	B2/C	LF	35 DFS
Ploysongsang et al. [18]	unknown	82	C	ENI	72 S
		41	C	LF	40 S
Harisiadis et al. [19]	unknown	48	C	ENI	64 S
		31	C	LF	61 S
Bagshaw [1]	pathologic	27	A/B	ENI	70 DFS
		30	A/B	LF	53 DFS

LF = Local field; DFS = disease-free survival; S = surgery.
NB: The above trials are *not* designed to confirm or refute benefit of ENI (see text).

RTOG 75-06, over 600 patients with stage C disease or with stages A2-B and involved pelvic nodes were randomized to receive pelvic irradiation followed by a boost to the prostatic bed or pelvic plus para-aortic irradiation followed by a boost to the prostatic bed [20]. In RTOG 77-06, nearly 500 patients with stages A2, B disease were treated to the prostate only or to the pelvis with a prostatic conedown [21]. Although the intentions of this collaborative group were noble, their efforts were doomed from the outset because of poor trial design that allowed inaccurate imaging determination of baseline nodal status [22]. Among the patients who had only radiographic staging of nodes, no differences existed when comparing those with clinically positive nodes to those who were clinically node-negative. Hanks et al. [16] have therefore emphasized that the methodology of the RTOG trials prevented the investigators from answering their own valid questions.

ENI: Pathologic Determination of Nodal Status. At Stanford University, a prospective trial was devised to evaluate elective irradiation of the 'next most vulnerable lymph node region' [23] among patients with pathologic documentation of lymph node status. For example, the pelvis was electively treated if pelvic lymphadenectomy was negative whereas the para-aortic nodes were treated if pelvic nodes were involved. Patients receiving prophylactic nodal irradiation had improved survival though the differences were not statistically significant, perhaps because of the small number of patients enrolled in the trial. A nonprospectively randomized experience has also been reported from Stanford [1] that showed a statistically significant survival advantage for early stage prostate cancer patients receiving irradiation treatment to the prostate

Table 2. Node-positive prostate cancer: impact of TNI

Series	Determination of nodal status	n	Tx	Disease-free survival, %	
				5 years	10 years
Lawton et al. [24]	radiologic/pathologic	56	EB	60	33
Paulson et al. [26]	pathologic	41	EB	40	–
Bagshaw [1]	pathologic	61	EB	45	20
Hanks et al. [16]	pathologic	86	EB	32	15
Lange et al. [28]	pathologic	36	RP + EB	69	–
Grossman et al. [35]	pathologic	42	^{125}I	35	14
Batata et al. [29]	pathologic	28	^{125}I + EB	21	–
Gervasi et al. [30]	pathologic	152	^{198}Au + EB	75	43

EB = External beam; RP = radical prostatectomy; ^{125}I = iodine implant; ^{198}Au = gold implant.

and first echelon lymphatic drainage versus treatment to the prostate and only its immediately surrounding tissue.

The database from RTOG studies 75-06 and 77-06 have been re-analyzed by Hanks et al. [16]. Patients with pathologically negative lymph nodes showed better 5-year survival and NED survival when compared to patients with pathologically positive nodes. These studies attest to the fact that the theoretical value of elective nodal irradiation will only reach fruition in the setting of pathologic documentation of nodal status.

Therapeutic Nodal Irradiation (TNI)

Series reporting TNI should also be viewed from the vantage points of the precise means used to determine lymph node status (table 2).

TNI: Unknown Nodal Status. At the Medical College of Wisconsin, Lawton et al. [24] used external beam irradiation to treat 56 patients with stage D1 adenocarcinoma of the prostate. For the entire group, the actuarial survival was 76% at 5 years and 33% at 10 years. Interpretation of the report is compromised because of the incomplete provision of data relative to grade, extent of local tumor and degree of nodal involvement. More importantly though, the majority of patients described (59%) had no pathologic confirmation of nodal involvement. While Lawton et al. [24] attribute their outcome to meticulous work-up, the staging of their patients does not exceed the standards of the process defined by a recent newsletter from the Patterns of Care Study [25].

TNI: Pathologic Nodal Status. Paulson et al. [26] reported the results of a prospective trial that randomized patients with D1 disease to extended field

radiotherapy (pelvis and para-aortic chimney) versus delayed hormonal manipulation (orchiectomy, or DES). Although the study demonstrated an initial advantage for extended-field radiotherapy (70 vs. 50% survival at 34 months; $p = 0.056$) the benefit had dissipated by 60 months. More impressive disparity was noted when the end-point of 'median time to first failure' was scored (23.9 months in the radiotherapy arm versus 12.2 months in the hormonal arm; $p = 0.02$).

Bagshaw [1] reported a 10-year survival of 20% for 61 patients with positive nodes who received extended-field irradiation after lymphadenectomy. It is possible that this finite long-term survivorship would have been improved if the analysis was restricted to patients with positive pelvic nodes (approximately 20% had positive para-aortic nodes in this report from Stanford) and if the lymph nodes were treated in continuous rather than interrupted fashion (which was done to minimize acute morbidity while the prostate was boosted).

Two institutions have used pelvic irradiation after radical prostatectomy among patients found to have involved pelvic lymph nodes. Bahnson et al. [27] reported a 41% 5-year recurrence-free survival with a 50-month median time to failure among 6 patients who received 50 Gy of adjuvant pelvic irradiation following surgery. Lange et al. [28] administered 45 Gy to the pelvis and 60 Gy to the prostatic bed of 36 patients with stage D1 disease after surgery. The actuarial 5-year survival was 69% but the 95% confidence intervals were quite wide ($\pm 18\%$) and recurrences were still being detected after 5 years. Small patient numbers, limited follow-up, absence of concurrent controls and potential for selection bias necessitate a cautious reading of these reports.

Interstitial irradiation has also been part of the armamentarium used to combat patients with involved nodes. The predominant experience from Memorial Sloan-Kettering Cancer Center (MSKCC) entailed bilateral pelvic lymphadenectomy followed by insertion of ^{125}I sources into the prostate in order to deliver a dose of 16,000 cGy over a 1-year period. In a recent update of the 345 patients so treated, Leibel et al. [pers. commun., 1993] found that by 10 years, less than one-third had survived and more than 80% had failed distantly. Two centers interstitially irradiated the prostate itself and added external irradiation to the nodes. In 1980, Batata et al. [29] added external beam radiotherapy (either to the pelvis or to the pelvis and para-aortic region) after pelvic lymphadenectomy and ^{125}I implantation. Twenty-eight patients treated in this manner derived no survival or local control advantage when compared to other patients treated at MSKCC via lymphadenectomy and brachytherapy alone. It is unclear why only these 28 patients were selected to receive supplemental external beam treatment and whether the blocking utilized in the radiation portals may have shielded disease. A similar concept was piloted by

Table 3. Node-positive prostate cancer: surgical management

Series	n	Tx	Disease free survival, %	
			5 years	10 years
Prout et al. [42]	32	RP	34	–
Smith et al. [36]	17	RP	29	–
Kramer et al. [38]	11	RP	0	0
	13	RP + DHT	0	0
Zincke et al. [31]	104	RP	48	38
	162	RP + EHT	84	80
Van Aubel et al. [41]	20	RP + EHT	50	–

RP = Radical prostatectomy; EHT = early hormonal therapy; DHT = delayed hormonal therapy.

Gervasi et al. [30] at Baylor University where the isotope used was radioactive gold (^{198}Au). Among 152 patients treated with this combined approach, the 5-, 10- and 15-year disease-survival rates were 75, 43 and 21%, respectively. It is difficult to understand how the Baylor experience for locoregionally advanced disease can appear superior to other strategies for node-positive prostatic cancer when methods similar to theirs yielded such poor results for early stage prostate cancer [7].

Lessons from Surgical Management

In general, the prognosis for node-positive patients managed by surgery alone is extremely poor; however, the results appear considerably improved when early hormonal therapy is coupled with radical prostatectomy (table 3). Hormonal manipulation seems to perturb disease progression by 5 years but it is not clear whether long-term survival is affected. Extended follow-up of these early reports will be needed to determine whether the advantages presumably imparted by adjuvant hormonal treatment can be sustained. Moreover, the relatively small number of publications concerning a relatively common disease suggests that the available surgical series reflect a bias to publish positive studies insofar as it is difficult to understand how patients with such advanced disease can have observed survivorship that surpasses the expected rate of survival for age-matched controls [31].

Several surgical series underscore the need for caution in considering data that do not incorporate PSA into NED calculations (table 4). For instance,

Table 4. Impact of PSA on NED survival

Series	Tx	NED survival (clinical)	PSA data
Steinberg et al. [32]	RP	83% at 5 years	3/22 NED at 3 years
DeKernion et al. [33]	RP	25% at 10 years	10% NED at 10 years
	RP + ET	40% at 10 years	25% NED at 10 years

NED = No evidence of disease; RP = radical prostatectomy; ET = endocrine therapy (leuprolide, estrogens, orchiectomy).

although Steinberg et al. [32] boast a 5-year NED survival of 83%, that finding belies the true prognosis of that cohort in whom only 3 of 22 patients had undetectable levels of PSA by 3 years posttreatment. Similarly, DeKernion et al. [33] observed a 10-year clinical NED rate of 25% that dwindled to 10% if PSA-based follow-up was employed. A parallel reduction in PSA-based NED survival was noted by DeKernion et al. [33] among their patients treated by combined surgery and endocrine manipulation.

Potentially Curable Subsets

Since the overall prognosis for prostate cancer patients with nodal involvement is poor, and the proposed therapeutic alternatives are often morbid, investigators have attempted to isolate subgroups of patients who are potentially curable for whom aggressive therapy can be justified. Grade carries tremendous prognostic significance in the treatment of organ-confined prostate cancer [34] and it is logical to assume that the same applies to prostate cancer metastatic to lymph nodes. Indeed, in the brachytherapy series from MSKCC [9, 35], the aggregate of patients with well- and moderately well-differentiated lesions exhibited a statistically significant survival advantage when compared to patients with poorly differentiated lesions.

For some pelvic malignancies that metastasize to lymph nodes, the stage of the primary tumor retains independent prognostic significance [39, 40]. In the setting of prostate cancer, however, analysis of outcome according to the stage of primary tumor [9, 29, 35, 36] uniformly discloses that the mere presence of nodal metastases obscures any impact of the extent of local tumor.

The weight of evidence (table 5) suggests that 'limited nodal involvement', defined in a variety of ways (e.g., solitary, microscopic, small volume), confers a favorable prognosis at 5 years. This observation appears to hold among diverse therapeutic approaches [31, 36–38, 41, 42].

Table 5. Influence of extent of nodal involvement on outcome

Series	n	Extent of nodal involvement	Outcome
Prout et al. [42]	11	solitary node	82% NED at 5 years
	21	multiple nodes	23% NED at 5 years
Smith et al. [36]	18	solitary node	44% NED at 5 years
	22	multiple nodes	27% NED at 5 years
Zincke [46]	21	solitary node	78% 5-year survival
	6	multiple nodes	68% 5-year survival
Steinberg et al. [32]	66	microscopic	80% 5-year survival
	54	macroscopic	40% 5-year survival
Barzell et al. [9]	18	small volume (<3 cm^3)	70% free of metastases at 5 years
	82	large volume (>3 cm^3)	10% free of metastases at 5 years

Finally, because these time-honored clinical parameters do not appear to have a decisive impact on outcome, many investigators have begun to probe more basic scientific prognostic markers. Flow cytometry, by virtue of its ability to document ploidy status, may prove quite valuable. For instance, in a small review by Winkler et al. [43], the unique results achieved with orchiectomy and radical prostatectomy by investigators at the Mayo Clinic [31] could be attributed to the presence of diploid tumors in the surviving node-positive patients. Whether such findings can be extrapolated to patients treated by primary radiotherapy remains to be seen.

Management Program for the Radiation Oncologist

Elective Nodal Irradiation

The rationale supporting ENI for prostate cancer remains strong despite the absence of validating scientific evidence. As noted earlier, data are available from the radiation oncologist's experience with squamous cell carcinomas of the cervix [3] and head/neck regions [4] as well as adenocarcinomas of the lung [5] and rectum [6] attesting to the merit of ENI. There is no reason to assume that the same concepts cannot be applied to prostate cancer.

When the risk of occult nodal involvement is relatively low, there is no need to electively irradiate the entire pelvis. As such, small conformal fields [45] are advocated for all A1 tumors and well-differentiated A2/B1 disease. Even in that setting, the radiation oncologist should be comforted by the knowledge that first echelon periprostatic nodes are treated. For disease with an unacceptably high likelihood of nodal metastases (e.g. C, moderately–poorly

differentiated A2, B1, B2), the management might consist of continuous course external irradiation to the pelvis (45 Gy minimum acceptable dose) followed by conformal conedown to the local tumor. Megavoltage beams should be directed through a four-field technique with all portals being irradiated daily.

Therapeutic Nodal Irradiation

Patients with small volume nodal disease (i.e., a solitary node especially if it contains <3 cm^3 of tumor, especially if only microscopic deposits) should be approached with definitive intent. Unresected positive pelvic nodes must receive at least 55 Gy. In the effort to sterilize these nodes, patients must be counseled about increased risks of treatment-related sequelae. If the involved nodes have been resected, a lower dose (e.g. 45 Gy) is advocated. Subsequently, localized fields are fashioned to deliver conedown boosts to the prostatic bed.

When large volume nodal disease is encountered, it is unlikely that curative strategies can be defended. These patients should all be offered hormonal manipulation (e.g. total androgen deprivation); further supplemental treatment (including radiotherapy) should be reserved for the protocol setting.

Future Directions

The many clinical dilemmas surrounding the issues of lymph nodes in prostate cancer mandate the development of clinical trials to resolve the controversies. The abortive effort of a large national group to settle the debate related to elective nodal irradiation [20, 21] will probably make it impossible to generate support for trials that probe the same important questions even if trial design is optimized. Despite this pragmatic obstacle, it is still logical to revisit the question of elective nodal irradiation as long as surgicopathologic nodal staging is required.

Regarding small volume (i.e. potentially curable) nodal disease, legitimate questions are being asked by those who favor primary surgical treatment and by those who favor primary radiotherapeutic treatment. If prostatectomy is selected as the local therapy, then the questions are whether to add early total androgen deprivation and/or postoperative irradiation. If primary external irradiation is chosen, then the phase III question becomes whether to add total androgen deprivation, especially in view of the persuasive results emerging from the RTOG studies of locally advanced prostate cancer [Hanks, pers. commun.]. Conversely, if large volume nodal disease exists, the starting point should be aggressive hormonal manipulation and the study questions relate to the need for treatment of the primary tumor at all (with surgery or irradiation)

and to what extent the local therapy should be delivered (e.g., ± elective nodal treatment).

Conservative estimates [2] suggest that at least 20,000 patients are annually diagnosed in the United States who are candidates for such trials. While reasonable investigators may differ on the precise framing of protocols, all physicians dedicated to eradication of the morbid and mortal effects of prostate cancer can agree that these patients should be encouraged to participate in this next generation of scientific studies.

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Nonseminoma Testicular Cancer: Surveillance versus Treatment

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Testicular cancer, although rare (affecting 3–6 men/100,000), is the most common malignancy in the 15- to 30-year age group. It is one of the most curable solid tumors. Improved diagnostic techniques, effective combination chemotherapy and the judicious use and timing of surgery have improved the cure rate to better than 90%.

Germ cell tumors account for 96% of all testicular cancer, the rest being Sertoli cell tumors, interstitial cell tumors, lymphomas and sarcomas. Pure seminoma accounts for 40% of all germ cell tumors while the nonseminomatous germ cell tumors – embryonal carcinoma, teratoma and choriocarcinoma or a combination of the different histologies with or without seminoma – account for 60%.

Mode of Spread

Testicular tumors spread most commonly through the lymphatic system, although pure choriocarcinoma, which accounts for 5% of all germ cell tumors, almost always metastasizes through the bloodstream because of its predilection for early vascular invasion. The lymphatic spread of testicular cancer occurs in an orderly fashion.

Lymphatic channels leave the testis at the testicular mediastinum together with the vessels, nerves and efferent tubules which carry the sperms towards the epididymis. Four to eight lymphatic channels travel along the spermatic cord through the inguinal canal into the retroperitoneum. The lymphatics from the right testis drain into the interaortocaval nodes at the level of the second lumbar vertebra. The lymphatics from the left drain into the left para-aortic

Table 1. Nonseminomatous testicular cancer

Primary stage	Incidence of lymph node metastasis, %	Survival with negative lymph nodes, %	Survival with positive lymph nodes, %
I	20	98	90
II	100	–	85
III	100	–	65

lymph nodes below the left renal vessels. From there, the lymphatics drain into the cisterna chyli then to the thoracic duct and into the left supraclavicular lymph nodes. In the presence of lymph node metastasis and obstruction of lymphatic channels, retrograde spread of tumor into the paracaval, preaortic or iliac lymph nodes may occur (table 1).

Extranodal metastasis, although rare, does occur and is usually due to either vascular invasion in the primary lesion or tumor microemboli through lymphatic-venous communications.

Staging

The most commonly used staging system is that proposed by the Royal Marsden Hospital. It is as follows:

Stage I: Tumor confined to the testis without clinical evidence of lymphatic spread or distant metastasis. Ten to 20% of patients with clinical stage I will have microscopic lymph node metastasis.

Stage II: Tumor spread into the retroperitoneal lymph nodes but not beyond. Stage II is subdivided according to the extent of retroperitoneal nodal involvement: IIA is nodal involvement of <2 cm in greatest dimension, IIB is between 2 and 5 cm and IIC is bulky retroperitoneal lymphadenopathy of >5 cm.

Stage III: Supraclavicular and/or mediastinal lymphadenopathy or extranodal metastasis to the lungs, liver, bone and brain.

Treatment

The standard treatment of clinical stage I nonseminomatous testicular germ cell tumors is radical orchiectomy followed by retroperitoneal lymph node dissection (RPLND). One of the major side effects of RPLND is the loss

Table 2. Nonseminomatous germ cell tumors: patient and tumor characteristics

	Surveillance	RPLND
Patients, n	28	23
Pure embryonal cancer	6	6
Mixed germ cell cancer	22	17
with choriocarcinoma	3	2
Elevated preorchiectomy		
α-fetoprotein	16	13
β-HCG	13	9
Microvascular invasion	0	3

of ejaculation and, therefore, sterility. This occurs because of the injury to the sympathetic nerves in the retroperitoneum during lymph node dissection. Since the majority of men who develop testicular cancer are young and may have not yet finished planning their future with respect to marriage and children, such a side effect can be devastating.

Effective chemotherapy and more accurate staging procedures have encouraged many centers to select a group of young men with clinical stage I disease and follow them after radical orchiectomy without RPLND. We reported on the results of our surveillance study in 1989 [1]. The following is an update.

Materials and Methods

Between 1981 and 1990, 28 men with nonseminomatous germ cell testicular cancers whose tumors were confined to within the tunica albuginea of the testis, who had normal postorchiectomy tumor markers (α-fetoprotein and β-HCG), and who had no abnormal findings on chest, abdominal and pelvic CT scans and bipedal lymphangiograms, were placed on surveillance after radical orchiectomy. They were followed with physical examination, tumor markers and chest radiographs every month for the first year, every 2 months for the second year, every 4 months for the third year and every 6 months thereafter. In addition, CT scans of the abdomen and pelvis were done at 3, 6, 9 and 15 months after orchiectomy. All patients have been followed for at least 2 years.

During the same period, 23 men who were treated with orchiectomy and RPLND because of abnormalities seen on either CT scans or lymphangiograms, or because of microvascular invasion in the primary tumor, and who were found to have negative nodes (pathologic stage I disease), were followed in the same manner except for the routine abdominal and pelvic CT scans. All patients have been followed for at least 2 years. Table 2 lists the patient and tumor characteristics of both groups.

Table 3. Recurrences

	Surveillance	RPLND
Total number of patients	28	23
Recurrences, n	4 (14%)	3 (13%)
Site of recurrences		
Retroperitoneum	3	0
Lung	1	3

Results

Four patients in the surveillance group (14%) had recurrence of disease, in the lung in 1 (at 3 months) and in the retroperitoneum in 3 (at 6, 8 and 9 months, respectively). Three of the 4 patients were treated with cisplatin-based combination chemotherapy and the fourth patient underwent RPLND. All 4 patients are alive without evidence of disease for at least 3 years from the end of therapy for the recurrent disease.

Three patients in the RPLND group (13%) developed recurrent disease, all in the lungs at 3, 3 and 6 months, respectively. All were treated with cisplatin-based chemotherapy and all 3 are alive and well for at least 4 years following treatment (table 3).

Discussion

The reported relapse rate in patients placed on suveillance after orchiectomy is between 16 and 35% [2–5]. The relapse rate in the present series is only 14% and is equivalent to the relapse rate in patients with pathologic stage I disease treated with orchiectomy and RPLND. This difference in the rate of relapse between the present series and what has been reported in the literature is due to patient selection (table 4). The series reporting high recurrence rates include patients with more locally advanced disease and tumors with microvascular invasion, two factors which were found to correlate significantly with the presence of microscopic lymph node metastasis [6].

We have shown that surveillance is a valid alternative to RPLND in a carefully selected group of young men with clinical stage I nonseminomatous testicular cancer. The selection criteria we recommend for placing a patient on surveillance are the following:

(1) Young men whose fertility is important to their family planning.

Table 4. Absolute criteria for surveillance

1. Tumor confined to within the tunica albuginea of the testis without microvascular or microlymphatic invasion
2. Normal postorchiectomy tumor markers
3. Normal CT scans of the chest, abdomen and pelvis
4. Normal lymphangiogram

(2) Patients with tumors confined to within the tunica albuginea of the testis without rete testes or epididymal involvement.

(3) Tumors which do not exhibit microvascular and microlymphatic invasion.

(4) Normal postorchiectomy tumor markers.

(5) Absolutely normal findings on CT scans of the chest, abdomen and pelvis.

(6) Absolutely normal lymphangiogram. We continue to perform bipedal lymphangiograms on patients considered for surveillance because of the improved detection rate that lymphangiograms provide. Six of our patients, who had been candidates for surveillance based on all other criteria, underwent RPLND because of abnormal lymphographic findings. Five of the 6 had microscopic lymph node metastasis which were not detected even on retrospetive review of the CT scans.

(7) Close follow-up with physical examination, chest radiographs and tumor markers every month for the first year, every 2 months for the second year, every 4 months for the third year and every 6 months thereafter. Since the rate of recurrence in our patients with pathologic stage I disease is the same as that in patients on surveillance, we recommend the same follow-up procedure for both groups. In addition, patients on surveillance should undergo abdominal and pelvic CT scans at 3, 6, 9, and 15 months following orchiectomy. All three recurrences in the retroperitoneum were detected by the routine follow-up CT scans.

Surveillance eliminates the need for RPLND in the majority of patients with clinical stage I nonseminomatous germ cell testicular cancer.

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Early Stage Testicular Seminoma: The Role of Radiation Therapy following Orchiectomy

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Testicular cancer is the most common malignancy among men aged 15–40. It accounts for approximately 5,000 new cancer diagnoses per year in the United States [1]. Of the testicular tumors, seminomas are the most common subtype, comprising nearly 60% of the germ cell total. With the advent of multidrug chemotherapy, which allows for cure of disseminated disease, the overall cure rate for all stages is now greater than 90% in most treatment centers. As seminoma patients are now most likely to become long-term survivors, it is mandatory to minimize the late sequelae of primary treatment.

Following inguinal orchiectomy, the evaluation for metastatic disease should include quantitative assays of serum markers, human chorionic gonadotropin (HCG) and α-fetoprotein, a chest x-ray and an abdominal CT scan. If the abdominal scan is positive, mediastinal and chest CT scans should be performed. If negative, a bipedal lymphangiogram is indicated for two reasons: firstly, it can detect abnormal para-aortic lymph nodes in 13–22% of patients with negative CT scans [2–4], and secondly, it provides the radiation oncologist with a clear map of the common iliac and para-aortic lymph nodes. This allows for optimal field shaping and maximal exclusion of nontarget normal tissues.

Standard Management of the Stage I and IIA Patient

The current standard treatment for stage I and IIA seminoma patients consists of orchiectomy followed by irradiation of the para-aortic and ipsilateral common iliac lymph nodes. Adjuvant irradiation is given to the draining

lymph nodes as seminoma spreads in a predictable and progressive fashion along the midline lymphatics. Whether to limit irradiation to the infradiaphragmatic region or extend it to include mediastinal and supraclavicular fossa regions has been the subject of past debate (see below). Radiation is given using conventional fractionation (150 cGy/day, 5 fractions/week) with 6–10 MV linear accelerator beams to a total dose of 25–30 Gy for stage I patients. For stage IIA patients, a boost dose to 36 Gy is recommended to the involved nodes with a 5-cm margin. The presence of anaplastic histology or elevated serum gonadotropins were previously judged by some to be an indication either to depart from standard therapy [5–7], or to consider systemic chemotherapy. This is no longer felt to be the case: Mirimanoff et al. [8] reviewed the records of 1,169 seminoma patients (of whom 132 had elevated HCG) and found that the production of HCG is not an unfavorable prognostic factor. Even among those patients with preorchiectomy HCG values 10–100 times greater than normal, prognosis remained excellent.

Adequate coverage of the renal hilum is important for left-sided tumors, since the testicular lymphatics on that side follow the testicular vein to its insertion usually into the left renal vein. For right-sided tumors, the lymphatic drainage is usually to the first echelon lymph nodes at the level of L3-L4, adjacent to the vena cava. Primary tumor invasion of the epididymis makes the ipsilateral internal iliac (hypogastric) lymph nodes a possible first echelon drainage site. These are therefore included in the treatment portals. Contralateral lymph node irradiation has been recommended for patients who have had ipsilateral orchiopexy or inguinal herniorrhaphy because of abnormal postsurgical lymphatic drainage. The need for this, however, is unclear [9–13]. The ipsilateral scrotum is considered target when the primary tumor invades part of the scrotum or if microscopic seminoma cells are judged to remain in the scrotum after removal of the seminoma through a scrotal incision. A 12–15 MeV electron beam field is matched to the lower border of the photon field. With proper positioning and blocking [14] the contralateral testicle can be moved more than 4 cm distance from the electron beam edge, and has consistently been measured to receive less than 3% of the electron dose by scatter [1].

The combination of orchiectomy and infradiaphragmatic radiation therapy for stage I disease yields relapse-free survival rates at 3 years and beyond in excess of 95% in nearly all reported series. For stage IIA disease, relapse-free survival is in the range of 85–100%. The very few stage I and IIA seminoma patients who do fail are usually salvaged with combination chemotherapy, and thus the ultimate cure rate is very close to 100%. With such excellent results, current research aims to study the careful reduction of treatment dose and/or volume while maintaining a high probability of cure.

Table 1. Cardiac disease with and without mediastinal irradiation (XRT)

Series	Cardiac disease	
	+XRT (%)	–XRT (%)
Hanks et al. [16]	8/152 (5.3)	2/220 (0.9)
Peckham and McElwain [17]	5/37 (13.5)	2/80 (2.5)
Lederman et al. [18]	6/58 (10.3)	0/66 (0)
Total	19/247 (7.7)	4/366 (1.1)

Controversies in Early Stage Disease

The Decline and Fall of Elective Mediastinal Irradiation (EMI)

EMI was previously given to patients with stage I and IIA seminomas in addition to irradiation of the infradiaphragmatic lymphatics. It was hoped that mediastinal irradiation would eradicate radiographically occult disease one to two nodal echelons beyond known disease and increase the likelihood of cure. EMI was not, however, without potential deleterious sequelae.

The Patterns of Care Survey for the treatment of seminomas was originally published by Hanks et al. [15] in 1981. Recently, the results have been updated to include 15-year follow-up on 387 patients treated in 1973 and 1974 [16]. With regard to stage I and IIA patients, Hanks et al. [16] found a significant increase in intercurrent disease and cardiopulmonary death among those patients who received EMI as compared to those who received only infradiaphragmatic irradiation. There was a 13% actuarial rate of cardiac death at 15 years for those who received EMI. Overall, there were 8/152 (5%) cardiac deaths among those who received EMI, versus 2/220 (1%) among those who did not receive EMI (table 1). Peckham and McElwain [17] also reported an increased incidence of cardiac deaths among those patients who received EMI (13.5%) as compared to those who did not (2.5%). In reviewing the patients treated at the Joint Center for Radiation Therapy, Lederman et al. [18] found postirradiation cardiac complications only among those patients who received EMI (10%). Both Lederman and Hanks found that those patients >40 years who received EMI were more likely to develop cardiac complications than those <40 years; however, it may simply be a question of time before the younger patients manifest any radiation-induced cardiac toxicity [16].

Radiation portals for seminoma patients often include a large proportion of the active bone marrow: infradiaphragmatic portals alone include 35–40% of the total [19]. However, it is when both infra- and supradiaphragmatic irradiation is administered that chemotherapeutic salvage can be compromised secondary to the harmful effects of the radiation on the marrow reserve. Ytredal and Bradfield [20] found bone marrow hypoplasia in their patients who received both infra- and supradiaphragmatic irradiation compared with those who received infradiaphragmatic irradiation alone. Einhorn [21] reported that the ability to deliver salvage chemotherapy to previously irradiated stage II patients was dependent upon the extent of prior irradiation. Patients previously irradiated and then treated with cisplatin, vinblastine and bleomycin (PVB) chemotherapy experienced major difficulties when the radiation portals had included both infra- and supradiaphragmatic nodes. Myelosuppression was prolonged and the incidence of bleomycin-activated pulmonary fibrosis increased. Friedman et al. [22] found that optimal doses of chemotherapy had to be attenuated in 4/6 patients previously treated with abdominal and mediastinal irradiation unlike patients who had been treated with abdominal radiotherapy: these were able to tolerate full-dose chemotherapy.

Therefore, one may conclude that the administration of EMI places the patient at a significantly increased risk for the development of cardiac toxicity and reduced bone marrow reserve. The latter may adversely affect a patient's tolerance to potentially curative chemotherapy in the event of radiation failure. What then are the benefits of EMI? More specifically, does EMI prevent the progression of distant disease as manifested by increased survival rates?

With the development of effective salvage chemotherapy, many began to question the survival advantage of EMI in early stage disease. Many cancer centers began treating stage I and IIA patients with infradiaphragmatic irradiation only. It was soon recognized that isolated mediastinal failure was a very uncommon event in these patients: approximately 2% for stage I and 3% for stage IIA (table 2). Herman et al. [23] reviewed 1,652 seminoma patients treated in 18 Canadian cancer centers between the years of 1960 and 1981. Treatment consisted of inguinal orchiectomy and para-aortic and pelvic lymph node irradiation only. Mediastinal relapses were found in 28/1284 (2%) of stage I patients, and 8/197 (4%) of stage IIA patients. Dorsoretz et al. [24] and Ball et al. [25] found similar relapse rates when mediastinal irradiation was withheld. Thomas et al. [9] reported a 87% 5-year actuarial survival rate for stage IIA patients treated with infradiaphragmatic irradiation alone. Only 3/40 stage IIA patients failed; none in the mediastinum. When compared with the reported series in which EMI had been used, they found similar failure and survival rates. They therefore concluded that EMI was not effective in preventing the development of distant disease and the survival advantage was negligible.

Table 2. Mediastinal and supraclavicular nodal relapses following infradiaphragmatic radiotherapy (number of relapses/number of patients)

	Stage I	Stage IIA
Thomas et al. [9]	6/338	0/40
Herman et al. [23]	28/1284	8/197
Ball et al. [25]	2/153	0/13
Dorsoretz et al. [24]	0/135	0/8
Total	36/1910 (1.9%)	8/258 (3.1%)

Since EMI subjects the patient to potentially lethal cardiac damage, possibly compromises chemotherapeutic salvage for radiotherapy failures, and offers no disease-free survival benefits, there is currently no indication to give it routinely to patients with stage I or IIA disease.

Elective Infradiaphragmatic Irradiation – Its Role Challenged

Toxicity of Elective Infradiaphragmatic Irradiation

Although infradiaphragmatic radiotherapy is generally considered 'mild' treatment, it (like mediastinal irradiation) is associated with a limited number of side effects. The acute toxicities of abdominal radiotherapy include transient nausea, vomiting and/or diarrhea in a small minority of patients [3, 24, 26–28]. Transient declines in platelet and WBC counts are frequently seen due to the volume of marrow irradiated. Severe acute complications are, however, rarely seen. Fossa et al. [29] found that the quality of life in postirradiation seminoma patients was similar to that of a healthy control group.

The most common symptomatic late effect is dyspepsia/ulcer disease, which develops in approximately 4–10% of patients [13, 26, 29, 30]. The risk is higher in patients who have undergone previous abdominal surgery, and it increases with higher doses of radiation [13, 29, 30]. Hamilton et al. [30] found, not surprisingly, that the development of peptic ulcer disease was more frequent in patients with pretreatment dyspeptic symptoms.

Fertility is of paramount importance given the young age of most patients and their near normal life expectancy. Spermatogenesis is affected by radiation in a dose-dependent fashion, with temporary oligospermia being seen in nearly all patients receiving 100 cGy or more (3% of total treatment dose) to the contralateral scrotum. With the appropriate combination of collimation and

blocking, scatter dose to the contralateral testis can be reduced to only 0.1% of the prescribed dose [14]. Coia and Hanks [31] reported a 12% postirradiation infertility rate in their series. The direct contribution of the scatter radiation to the infertility was unclear. Fossa et al. [32] examined the effects of ionizing radiation as reflected in sperm counts and FSH levels. This study confirmed previous observations that only one-third of seminoma patients are normospermic following unilateral orchiectomy and before further treatment. No significant correlation was noted between gonadal dose and posttreatment FSH. Patients who were azoospermic or severely oligozoospermic before treatment tended to maintain low sperm counts 2–3 years after radiotherapy. Fossa et al. [32] attributed this to abnormal pretreatment spermatogenesis rather than gonadal dose, as long as the dose is below 100 cGy. Despite this reassuring data, keeping the gonadal dose as low as possible by careful shielding is indicated to minimize the additional risks of teratogenesis and carcinogenesis [14].

Teratogenesis following low-dose gonadal irradiation is a frequently cited concern. The spermatids and spermatocytes are more radiosensitive than spermatogonia with regard to mutagenesis [33]. Low levels (2–5 cGy) of gonadal irradiation will not affect fertility, although sublethal genetic damage may be present within the spermatozoa [33–36]. Patients should be advised to wait at least 1 year before attempting to procreate, so as to minimize the risk of radiation-induced teratogenicity [37]. This delay likely allows for at least some repair of genetic damage in stem cells and the clearance of radiation-damaged spermatocytes and spermatids [14].

Second tumors have been reported with increased frequency among seminoma patients, and the question of radiation induction has arisen. Some have reported a two-fold increase in the risk of developing a second cancer following the diagnosis and treatment of testis cancer [38, 39]. Hellbardt et al. [40] found an increased incidence of cancer in both radiated and nonradiated tissue (table 3). With a median follow-up of 8 years, 11/116 patients had developed 12 second tumors: 5 solid tumors, 2 lymphomas, 2 leukemias and 3 contralateral seminomas were reported. However, when the seminomas were excluded, the incidence of second tumors was not significantly higher than expected.

In the 15-year follow-up of the Patterns of Care Survey, Hanks et al. [16] found a tripling in the incidence of second tumors and a doubling in the second cancer death rates (relative to expected rates for age-matched general population). At 15 years, there was an 8% actuarial rate of second cancers. The tumors arose in both radiated and nonradiated tissue with similar incidence. The cancers consisted of 10 solid tumors and 2 leukemias. The mean time to second cancer was 10.3 years. Interestingly, there was an equal incidence of second

Table 3. Second tumors

Series	Patients n	Total second tumors %	Nontestis second tumors, %	In-field tumors %	Leukemia or lymphoma %
Hay et al. [41]	517	11	9.8	3.8	0.6
Hellbardt et al. [40]	116	10.3	7.8	3.4	3.4
Hanks et al. [16]	372	3.8	3.5	1.6[1]	0.5

[1] Includes 5 marginal in-field second tumors.

tumors in those who received mediastinal irradiation (4%) and those who received only abdominal irradiation (4%).

Hay et al. [41] reported the findings of a retrospective review of 517 Scottish patients aged 15–84 who were treated for testicular tumors between 1950 and 1969. With a mean follow-up of 15 years, he found an increased risk of second tumors in both irradiated (relative risk: 1.94) and nonirradiated (relative risk: 1.99) tissue. There was an increased incidence of transitional cell cancers of the upper and lower urinary tract (7/517) within the irradiated volume and skin tumors (8/517) outside the treatment volume. Two leukemias and one lymphoma were observed. The mean dose of radiation was 30 Gy in 20 fractions, with no significant difference in the mean dose among those who developed second tumors and those who did not.

Kleinerman and Lieberman [42] reviewed 1,446 men registered in the Connecticut Tumor Registry between 1935 and 1982. Fifty-eight percent of the men received radiation. Some patients did receive chemotherapy, although the exact number was not stated. With the benefit of 8-year follow-up, they found a twofold increased risk of second cancers in both irradiated and nonirradiated men. Specifically, there was a threefold increased risk of second cancers in men <40 years, and a 1.7 increased risk of second cancers in men >40 years. An increased incidence of leukemias (8/1,446) was noted in both irradiated and nonirradiated men (relative risk: 5.2). An unspecified number of patients developing leukemia received chemotherapy.

It therefore appears that a two- to threefold increased risk of second tumors (and perhaps leukemias) exists for men with seminoma; however, this appears to be an unlikely consequence of radiation therapy alone. Rather, like so many other cancer patients, seminoma patients may have a predisposition to the development of second tumors independent of treatment [43]. Radiation oncologists, however, must not be complacent. Radiation is a well-recognized carcinogen [43], and since radiation-induced cancers may develop

decades after irradiation, it is best to minimize radiation exposure whenever possible.

Although infradiaphragmatic radiation is generally well tolerated with rare long-term deleterious sequelae, some clinicians (and some patients) have proposed surveillance or chemotherapy rather than subdiaphragmatic irradiation for stage I seminoma patients.

Chemotherapeutic Alternatives

Oliver [44] cites an 83% durable remission rate achieved with single-agent platinum compounds in the treatment of seminomatous germ cell tumors. He has therefore proposed clinical trials evaluating two cycles of the less toxic cisplatin analogue, carboplatin, as an alternative to radiation therapy. This proposal has its limitations: firstly, it is based on small phase II studies only; secondly, cytotoxics still carry uncertain risks of infertility and leukemogenesis, and thirdly, although the initial response rates to single-agent carboplatin are comparable to combinational regimens, the durable response rates, at least in advanced disease, may be inferior. MacVicar and Horwich [45] reported a 24% relapse rate in advanced seminoma patients treated with carboplatin alone. Fifty percent of all relapses were in previously affected and/or adjacent nodal groups. Thus, carboplatin is unproven as an effective alternative to platinum-based combinations. Since the more toxic cisplatin would be inappropriate for the >80% of stage I patients cured by orchiectomy alone, chemotherapy, for early stage disease, remains experimental.

Surveillance

It is generally believed that the incidence of occult metastases to the para-aortic nodes in stage I seminoma is approximately 10–20% (see below). Some, however, feel that it may be much less: Maier et al. [46] reported an 8% incidence of occult disease in the para-aortic lymph nodes based on retroperitoneal lymph node dissection studies for stage I seminoma patients. Surveillance has been successful in the treatment of nonseminomatous germ cell tumors [47–52]. However, seminomatous germ cell tumors differ in two important ways: firstly, there is no sensitive serum marker for seminoma, making it difficult to detect small volume relapse; secondly, the more protracted natural history of seminomas requires more prolonged surveillance. Nonetheless, several studies have been published where stage I seminoma patients were treated with orchiectomy alone. Initially, relapse rates were low, ranging from 4 to 13%. However, with further follow-up the rates increased to 10–20% (table 4). Most relapses occur within the first 2 years. However, relapses have been seen at 5 years [G. Thomas, pers. commun.]. Specht et al. [53] reported on the surveillance experience of the Danish Testicular Cancer Study Group. From

Table 4. Postorchiectomy surveillance

Series	Patients n	Follow-up (median)	Relapses (total) %	Relapses below diaphragm
Specht et al. [53]	261	48 months	18.8	48/49
Thomas et al. [59]	119	NA	5.9	6/7
Horwich et al. [54]	103	62 months	16.5	16/17
Allhoff et al. [60]	33	48 months	9.1	2/3

1985 to 1987, 261 stage I seminoma patients were treated with orchiectomy alone. With a median follow-up of 4 years, 49/261 (19%) patients recurred: 48/49 were subdiaphragmatic. Horwich et al. [54] have recently updated the Royal Marsden Hospital experience with 103 stage I seminoma patients seen at the RMH between 1983 and 1988 who were treated with orchiectomy alone. Surveillance consisted of outpatient clinical assessment every 2 months for the first year, every 3 months for the second year, and every 4 months for the third year and thereafter. In addition, each patient received an annual CT scan. With a 5-year median follow-up, 17 (18%) patients have relapsed: 16/17 within the para-aortic nodes, and 4/17 with large volume disease. Twelve of 17 were initially managed with infradiaphragmatic irradiation alone, of whom 4 developed a second recurrence in the mediastinum or supraclavicular fossa and thus received chemotherapy. Therefore, due to the bulk or extent of their recurrence, 8/17 required chemotherapy to control their disease. Most of the relapses occurred within 3 years of orchiectomy and initially within the para-aortic lymph nodes. The authors evaluated the predictive value of lymphatic invasion or vascular invasion for recurrence and found that only when the two were combined was there even a trend toward significance. Others have also looked at vascular invasion and not found this pathologic feature to be significantly associated with an increased risk of occult metastatic disease [55]. Horwich et al. [54] concluded that because of the difficulty in identifying patients at risk and detecting early relapse, surveillance for stage I seminoma should remain a research tool.

Infradiaphragmatic Radiation Fields: To Reduce or Not Reduce?

Although the current standard radiation field for early stage disease includes the para-aortic and ipsilateral pelvic lymph nodes, some have proposed that the pelvic lymph nodes be eliminated from the radiation field [16]. The reasons for field reduction are several: firstly, the normal lymphatic drainage of the testis bypasses the pelvic lymph nodes; secondly, a field

reduction would decrease the myelosuppression seen with marrow irradiation; thirdly, although no proof for cancer induction exists, less radiation is always preferred; fourthly, gonadal toxicity would be reduced, and finally, results from the surveillance studies suggest that nearly all early stage disease recurs in the para-aortic lymph nodes only.

The Medical Research Council is currently conducting a trial comparing full standard 'dog leg' irradiation (including the ipsilateral ileoinguinal lymph nodes) with irradiation only to the para-aortic region. Over the past 2 years, more than 400 patients (without history of pelvic surgery) have been accrued and, to date, none have recurred in the pelvic lymph nodes [A. Horwich, pers. commun.]. As with surveillance, more time is needed to see if this trend is sustained. Nonetheless, the results are interesting.

Radiation Dose: To Reduce or Not Reduce?

In the past, doses in the range of 40 Gy had been given to stage I and IIA seminoma patients with good results [13]. However, due to the tumor's exquisite radiosensitivity, doses of that magnitude were found unnecessary: Thomas [56] reported a 99% disease-free survival rate in 150 stage I seminoma patients treated to 25 Gy in 20 fractions. Hamilton et al. [57] reported a 100% disease-free survival rate in 232 stage I seminoma patients treated to 30 Gy. In view of these findings, the 1989 International Consensus Conference in Leeds recommended a dose prescription of 25 Gy in 20 fractions for stage I disease [58]. We prescribe doses of 30 Gy in 150-cGy fractions. This is effective in eradicating radiographically undetectable retroperitoneal disease with negligible long-term morbidity (see above).

Conclusions

Patients with stage I disease have an approximate 10–20% incidence of occult metastatic disease to the retroperitoneal lymph nodes; thus 80–90% of these patients do not actually require adjuvant nodal irradiation. It is not possible to discriminate those who require treatment from those who do not. The current philosophical trend in the management of early stage disease, therefore, is toward limiting adjuvant treatment to the minimum necessary to maintain high cure rates with low morbidity:

(1) Mediastinal irradiation is no longer indicated. It was associated with an increased incidence of intercurrent illness, cardiac disease, and myelosuppression. The survival benefits were negligible.

(2) Standard doses have been reduced to 25–30 Gy for stage I and 36 Gy for stage IIA disease.

(3) Elective para-aortic and pelvic lymph node irradiation remains the standard of care for stage I disease. In view of the low probability of pelvic nodal metastases from a testicular primary, it may prove possible to limit irradiation to a para-aortic field only. This is currrently under investigation.

(4) Discontinuation of infradiaphragmatic radiotherapy altogether has also been proposed. Surveillance studies of stage I patients have been limited by the difficulty in identifying patients at risk and detecting early relapses in the 10–20% who will recur. The evaluation of single-agent carboplatin has been proposed as a low toxicity alternative to radiotherapy for early stage disease. Until the results of appropriate randomized studies are available, infradiaphragmatic radiotherapy remains the standard of care for stage I and IIA disease.

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Can Patients with Regional Metastases from Carcinoma of the Endometrium Be Cured with Radiation Therapy?

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Lymphatic Drainage of the Uterus

The uterus is drained by lymphatic networks at the base of the endometrium, in the myometrium, and in the subserosa [11]. There are no lymphatics in the superficial parts of the endometrium. The principal collecting trunks pass outward at the uterine isthmus, extend along the course of the uterine vessels and drain primarily into the external iliac nodes.

Drainage from the uterine body differs from that of the cervix in three ways: (1) In the region of the fundus, lymphatics are more likely to pass with the ovarian lymphatics directly to the para-aortic nodes. On the left side the ovarian lymphatics drain primarily to nodes situated between the left ovarian and left renal veins. On the right side these lymphatics drain to nodes located between the right renal vein and the inferior vena cava. Shorter pathways from the fallopian tubes and fundus may also lead directly to the hypogastric, lower para-aortic, or common iliac nodes. (2) Lesions of the uterine fundus are less likely to drain to the ureteral and sacral nodes than those of the cervix. (3) Occasionally lymphatics from the fundus may extend along the inguinal ligament directly to the femoral nodes.

Table 1. Relationship between grade, depth of myometrial invasion, and incidence of lymph node metastasis [4]

Depth of invasion	Grade	Patients	With nodal metastases, %	
			pelvic	aortic
None	1	44	0	0
	2	31	3	3
	3	11	0	0
Inner third	1	96	3	1
	2	131	5	4
	3	54	9	4
Middle third	1	22	0	5
	2	69	9	0
	3	24	4	0
Outer third	1	18	11	6
	2	57	19	14
	3	64	34	23

Features Associated with Regional Metastases of Uterine Carcinomas

The overall incidence of regional metastasis associated with endometrial carcinomas is small. In the most comprehensive study of regional spread to date, the Gynecologic Oncology Group (GOG) reported that lymph node metastases were found in 70 of 621 patients (11%) with clinical stage I carcinoma of the endometrium. Of these 70, 36 (51%) had pelvic node involvement without evidence of para-aortic spread, 22 (31%) had both pelvic and para-aortic node involvement, and 12 (17%) had only evidence of para-aortic node involvement at laparotomy and selective lymph node sampling. However, even studies that report results of surgical staging underestimate the true incidence of regional spread. The likelihood of detecting small micrometastases may depend on how a specimen is handled and sectioned by the pathologist. In the GOG study, extensive lymph node dissection was not routinely performed, and the extent of nodal sampling varied.

A number of clinical and histological features are associated with lymph node metastasis. Both high-grade and deep myometrial penetration by tumor are associated with an increased incidence of lymph node metastasis (table 1). In the study by Creasman et al. [4], 60% of the cases with pelvic nodal metastasis and 70% of those with aortic node metastasis were among the 139 of

621 patients (22%) who had deep (outer third) myometrial penetration. Other factors strongly associated with nodal involvement in the Creasman study were positive peritoneal cytology ($p < 0.0001$), invasion of the uterine isthmus or cervix ($p = 0.01$), adnexal involvement ($p = 0.0001$), and capillary-like space involvement ($p = 0.0001$).

Although positive peritoneal cytology is correlated with lymph node involvement, this finding does not necessarily imply a poor prognosis. Kadar et al. [8] reported that positive peritoneal cytology did not significantly influence survival if the disease was otherwise confined to the uterus ($p > 0.2$), but did strongly influence prognosis if disease was also found in the adnexa, peritoneum, or lymph nodes ($p < 0.01$). At 5 years, the survival rate of patients who had positive cytology without extrauterine involvement was approximately 90%.

Schink et al. [14] have also reported a strong association between the diameter of an endometrial tumor and nodal metastasis. In their study, 40% of patients with tumors involving the entire endometrium had lymph node involvement, compared with 22% of those with less extensive tumors >2 cm in diameter and only 6% of those with tumors ≤ 2 cm. Although there was some correlation between tumor diameter, grade, and depth of myometrial infiltration, tumor diameter was still found to be an independent predictor of prognosis in multivariate analysis.

Relationship between Lymph Node Involvement and Survival

In 1991, Morrow et al. [10] reported on the relationship between surgical-pathologic risk factors and outcome in 895 patients with clinical stage I and II carcinoma of the endometrium who were entered on a large GOG trial. In addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy, patients underwent surgical staging with selective pelvic and aortic node sampling, peritoneal washings, and abdominal inspection. Although this study is currently the only large published experience with relatively consistent surgical staging in patients with endometrial cancer, as discussed above, the extent of nodal sampling was not clearly defined, and the results undoubtedly represent an underestimate of the incidence of lymph node involvement. Nevertheless, the authors reported a strong correlation between documented lymph node involvement and outcome. At 5 years, the recurrence-free survival rate of patients without known lymph node metastasis was approximately 85%, compared with 70% for those with pelvic node involvement without known aortic node metastasis and 36% for those with aortic node involvement. This survival rate of 36% for patients with aortic node involvement treated with

Table 2. Survival rate of patients treated with extended field irradiation for endometrial carcinoma metastatic to para-aortic nodes

Reference	Five-year survival, %
Komaki et al. [9]	60
Blythe et al. [2]	57
Potish [12]	40
Feuer and Calanog [6]	50
Morrow et al. [10]	37
Rose et al. [13]	53
Corn et al. [3]	46

Table 3. FIGO surgical staging system for carcinoma of the uterine corpus (1988) [7]

Stage	Characteristics
IA G123	Tumor limited to endometrium
IB G123	Invasion to $<1/2$ myometrium
IC G123	Invasion to $>1/2$ myometrium
IIA G123	Endocervical glandular involvement only
IIB G123	Cervical stromal invasion
IIIA G123	Tumor invades serosa or adnexae or positive peritoneal cytology
IIIB G123	Vaginal metastases
IIIC G123	Metastases to pelvic or para-aortic lymph nodes
IVA G123	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph node

extended field radiation therapy agrees with the results of other small published experiences with treatment of similar patients (table 2).

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgical staging system (table 3) incorporating some of the known important histopathologic prognostic indicators. In this system, all patients who have pelvic or para-aortic node metastasis without evidence of hematogenous or intraperitoneal spread are classified as stage IIIC. Although this system does separate some individuals with unfavorable features, in some ways the change unfortunately confuses the situation even further. The extent

of nodal sampling and handling of the surgical specimen are not consistent among institutions, making it extremely difficult to compare treatment results. When relatively aggressive nodal dissections are used, the apparent survival rates of all stage groups are likely to appear better simply because patients with minimal nodal spread will be moved from stage I and II (improving the composition of those groups) to stage III (also improving the composition of stage III because such patients will be among the most favorable of patients with regional spread). In this classic example of the Will Rogers phenomenon [5], institutions that search aggressively for regional disease may erroneously appear to achieve better results than those that employ more selective sampling techniques.

The new staging system places patients with pelvic and aortic nodal involvement in the same category – stage IIIC – although the prognosis of these two groups is quite different. The system also places all patients with positive peritoneal cytology in stage IIIA although, as discussed above, some subsets of patients with positive cytology may have excellent prognoses with 5-year survival rates of 80% or better. Because these patients are all labeled as stage III, there may be a tendency to group them together therapeutically, thus potentially including patients with relatively favorable prognoses on very aggressive treatment protocols. This can only be avoided by evaluating patients individually in the light of current knowledge about important prognostic variables.

The Influence of Regional Radiotherapy on Outcome

Although many efforts have been made to evaluate the role of pelvic radiotherapy on outcome of patients with endometrial carcinoma, most studies have failed to document an influence of radiotherapy on survival – at least in part because they included inadequate numbers of patients and numerous biases in the selection of treatment. The GOG outcome analysis [10] reported a 70% 5-year survival rate in patients who had documented pelvic node involvement without evidence of aortic node involvement. Unfortunately the treatment given to these patients was poorly documented because the study was not intended to evaluate the efficacy of any given treatment. However, the authors do state that most patients with pelvic nodes were treated with pelvic irradiation. Since the nodes were not dissected with therapeutic intent, it is tempting to conclude that radiotherapy was responsible for the excellent survival rate in this unfavorable group of patients. However, because there is no published experience with observation of patients without adjuvant irradiation following documentation of nodal disease, we have limited information about the natural history of the disease in this setting.

Table 4. Patterns of failure in Norwegian Radium Hospital randomized study of the role of postoperative pelvic radiation therapy (RT) in clinical stage I uterine carcinoma [1]

Myometrial invasion	Treatment group	Patients, n	Deaths of cancer		Pelvic relapse, %	Distant metastasis, %
			n	%		
≤50%	No pelvic RT	162	6	4	4	3
	Pelvic RT	178	17	10	2	10
>50%	No pelvic RT	102	18	18	15	10
	Pelvic RT	76	11	15	7	12

To date, only one prospective randomized study has assessed the role of pelvic radiotherapy. In 1980, Aalders et al. [1] published the results of a study conducted at the Norwegian Radium Hospital that randomized 540 patients with clinical stage I endometrial carcinoma either to receive 40 Gy of pelvic irradiation or to receive no further treatment after TAHBSO and vaginal radium. Although the study documented a decreased pelvic recurrence rate in patients who received pelvic irradiation, there was no significant difference in overall disease-specific survival, presumably because of an increased rate of distant metastasis in the radiotherapy arm. Subset analysis of patients with deeply invasive grade 3 disease did suggest a survival advantage when radiotherapy was given, although this result did not quite achieve statistical significance and is subject to the usual criticisms of subset analysis.

However, the details of this study illustrate some of the reasons why it has been so difficult to evaluate the efficacy of adjuvant treatment in this disease. Because the overall survival rate of patients with endometrial carcinoma is excellent (~80%) after hysterectomy alone, the margin for improvement is small and many patients are needed to demonstrate improved survival with added treatment. Although the Norwegian study is one of the largest published series of patients with endometrial cancer, the actual number of patients with high-risk disease was relatively small as was the number of disease-related deaths. As a result, the study probably had an inadequate number of patients to demonstrate moderate differences in survival between patient subgroups. The authors suggest that the improved pelvic control achieved with pelvic irradiation was not translated into survival because patients whose pelvic disease was controlled with irradiation failed distantly. However, their data show that almost all the advantage in local control was in the patients with deep myometrial invasion, whereas most of the excess in distant metastases was in patients with superficial or no muscle invasion (tables 4, 5). The absence of

Table 5. Patterns of failure in Norwegian Radium Hospital randomized study of the role of postoperative pelvic radiation therapy (RT) in clinical stage I uterine carcinoma – patients with grade 3 disease [1]

Myometrial invasion	Treatment group	Patients, n	Deaths of cancer		Pelvic relapse, %	Distant metastasis, %
			n	%		
≤50%	No pelvic RT	36	3	8	6	6
	Pelvic RT	47	8	17	2	17
>50%	No pelvic RT	51	14	28	20	16
	Pelvic RT	44	8	18	5	14

histologic subtyping in this study, which was completed before the aggressive natural history of uterine papillary serous carcinoma was identified, also confuses interpretation of the results.

Ultimately the role of pelvic irradiation can only be documented by a randomized prospective study that includes a large number of carefully stratified patients with high-risk factors such as deep myometrial invasion and positive pelvic nodes. Although there continues to be controversy about the influence of pelvic irradiation on survival, it may not be possible to conduct such a study in this country because practitioners are unwilling to withhold pelvic irradiation from patients with positive nodes in view of the improved pelvic control rates and excellent survival rates reported for patients who do receive pelvic irradiation. However, in all cases, particularly those with intermediate risk factors, the advantages of pelvic irradiation must be carefully balanced against the risk of treatment-related complications.

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Management of Lymph Node Metastasis in Carcinoma of the Cervix

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The invitation to author this chapter has motivated me to take a fresh look into the problem of lymph node metastasis in carcinoma of the cervix – in a way that we radiotherapists usually do not do in our practice. Traditionally we have concentrated on treating the primary lesion, with fields that also encompass the pertinent pelvic nodes. The medical literature, other than surgical writings, has not been rich in reports related to lymph node metastasis in this disease. However, the emergence of the Gynecologic Oncology Group (GOG) protocols and those of other groups has permitted far more precise evaluation of the status of the lymph nodes in cervix cancer, and gives new opportunity to evaluate their importance in cervix cancer management.

My acquaintance with carcinoma of the cervix started in the mid-1950s. Since, many of the concepts of the disease have changed, including our concern for the involvement of regional lymph nodes with malignancy. In the mid-1950s, cancer of the cervix accounted for 25% of cancer in all Puerto Rican women, and 50% in the 30- to 40-year age group. Intraepithelial lesions (stage 0) were 5% of the case load, whereas stage III cases were the predominant group. Fortunately, with the public health programs that we were able to conduct, the percentage of stage 0 cases has increased to over 60% of diagnosed patients, the percentage of advanced lesions has decreased, and a reduction in mortality of close to 80% has occurred.

The magnitude of the problem of carcinoma of the cervix in the USA can be seen in table 1. The estimated number of women expected to be diagnosed for the first time with this invasive tumor in the year 1994 is 15,000. In the last 30 years we have observed a constant reduction in incidence of the invasive forms and the mortality from this disease: a 69% reduction in tumor mortality has occurred in the USA during this period [1]. Needless to say, the judicious

Table 3. Lymphangiogram in adenocarcinoma of the cervix [from 3]

Patient group	Stage			
	IB <3 cm	IB >3 cm	II	III
Total	92	125	63	61
Patients who had lymphangiogram	31	68	40	41
Patients with positive lymphangiogram (%)	0	17 (25)	12 (30)	24 (51)

Table 4. Para-aortic node evaluation; percentage of false negative images [from 2]

Group	n	%
Study patients	320	
Completed all studies	264	83
False negative		
Lymphangiogram	12	8.2
CT	40	17.8
Ultrasound	44	21.7

resonance or sonography. In a GOG trial comparing diagnostic methods in 320 patients (83% completed all of the studies), lymphangiogram gave the lowest percentage of false negatives (8.2%) and ultrasound gave the highest (21.7%) (table 4). Surgical exploration was used as the standard for final diagnosis of metastatic pelvic and para-aortic nodes. The extra-peritoneal approach to para-aortic and pelvic node surgical evaluation has been associated with less radiation-induced morbidity than the transperitoneal approach.

Yield of Surgical Evaluation of Lymph Nodes

Pelvis and Para-Aortic Areas

The GOG data on the evaluation of pelvic and para-aortic nodes in carcinoma of the cervix by surgical technique is shown in table 5. This is based

Table 5. Exploratory laparotomy findings (GOG data) in stage IB squamous cell carcinoma [modified from 4]

Findings	Patients	
	n	%
Gross disease beyond the uterus, or involvement of the aortic nodes	87/732	12
Disease outside the pelvis		
Positive aortic nodes, microscopic or gross	29/732	4
Negative aortic nodes, gross involvement of other structures	7/732	1
Disease confined to the pelvis		
Pelvic tumor implants, direct extension or gross serosal breakthrough	32/732	4
Gross pelvic nodes only	19/732	3
Positive microscopic pelvic nodes in patients with none of the above findings	100/645	15.5

on 732 patients with stage IB tumors of squamous cell histology. Gross tumor outside of the uterus or microscopic para-aortic node metastasis was found in 12% (87/732). (Tumor beyond the pelvis with negative para-aortic nodes was found in only 1% of patients.) Six hundred and forty-five patients with no gross disease outside the uterus and negative para-aortic nodes had 15.5% microscopically positive pelvic nodes. With the addition of 19 patients with gross nodes, their reported overall incidence of pelvic lymph node metastases is 16% (119/732). There is no significant increase in the incidence of nodal metastasis in nonepidermoid cancers [5].

Scalene Area

Neck palpation often can detect scalene node enlargement. When these are palpable, the positivity of a scalene node biopsy will be close to 100%, particularly in the presence of positive para-aortic nodes. Table 6 shows that the overall positivity of scalene nodes ranges from 25 to 28% when positive para-aortic nodes are present. If positive para-aortic nodes are identified, a scalene node biopsy should be taken prior to embarking on radical treatment to the para-aortic chain – the presence of positive scalene nodes denotes distant metastases and para-aortic node irradiation cannot improve survival.

Table 6. Scalene node metastases in cervical carcinoma with positive para-aortic nodes

Reference	Patients, n	Positive scalene nodes	
		n	%
Vasilev and Schlaerth [6]	99	28	28
Stehman et al. [7]	44	11	25

Table 7. Incidence of pelvic node metastases (GOG data) in 732 patients with squamous cell carcinoma [from 4]

Patient group	Pelvic node metastases	
	n	%
All patients	119/732	16
Occult primary tumor	15/168	8.9
Gross primary tumor	85/477	20.9
Tumor diameter > 3 cm	35/152	23
Parametrial extension	19/44	43.2
Outer third of cervix invasion	69/227	26.4

Factors Associated with Lymph Node Metastases

The incidence of positive pelvic nodes in stage I squamous carcinoma can be affected by the factors shown in table 7. The reported incidence was lowest in patients with occult lesions, 8.9% (15/168), but went up to 20.9% (85/477) when the tumor was grossly evident. In lesions > 3 cm the incidence of nodes was 23% (35/152) in contrast with 12.7% (8/63) when the tumor diameter was 0.1–1.0 cm. The highest incidence was found when the parametrium was invaded, when 43.2% (19/44) of patients showed positive pelvic nodes versus 13.5% (81/599) when no parametrial invasion was present. Histological grade 1 tumors had 9.7% (9/93) pelvic node metastasis, 13.9% (52/373) in grade 2, and 21.8% (39/179) in grade 3. Depth of invasion expressed in millimeter penetration or by third of invasion (table 8) influenced the incidence of pelvic nodes. When no capillary lymphatic spaces were invaded by tumor, 8.2% (30/366) had positive pelvic nodes versus 25.4% (70/276) when these spaces contained tumor.

Table 8. Depth of cervix invasion [from 4]

Depth of invasion	Pelvic node metastasis		
	n	%	
≤5 mm	6/177	3.4	
6–10 mm	36/238	15.1	p = 0.0001
11–15 mm	30/135	22.2	
16–20 mm	19/49	38.8	
Inner third	9/199	4.5	
Middle third	28/210	13.3	p = 0.0001
Outer third	60/227	26.4	

Table 9. Incidence of para-aortic node metastases

Stage	Ref.	Patients, n	Para-aortic node metastasis	
			n	%
IB ≤3 cm	8	125	2	1.6
IB	9	866		4.7
IB	10	540		6
IIA	9	95		8.4
IIA	10	99		13
Barrel-shaped	11	43	15	34.8
IIB	10	494		19
IIIB	10	445		29

The incidence of para-aortic node metastases in stage 1 and IIA cases is shown in table 9. Stage IB lesions ≤3 cm in diameter showed 1.6% para-aortic node metastases versus 8.4% in stage IIA and 34.8% in barrel-shaped lesions. The significance of the various factors associated with pelvic node metastases is shown in table 10.

Prognostic Importance of Node Metastasis

The presence of lymph node metastasis influences various clinical parameters in carcinoma of the cervix. The rates of tumor recurrence and distant metastasis are increased and survival is diminished. At the University of Miami, tumor recurrence rates varied from 32.1% when the pelvic nodes were

Table 10. Factors associated with microscopic pelvic lymph node metastases (GOG data) [modified from 4]

Factor	Positive pelvic nodes		p
	n	%	
Gross primary tumor			
Occult	15/168	8.9	0.009
Gross	85/477	20.9	
Histologic grade			
1	9/93	9.7	
2	51/373	13.9	0.01
3	39/179	21.8	
Depth of invasion			
Inner third	9/199	4.5	
Middle third	28/210	13.3	0.0001
Outer third	60/227	26.4	
Parametrial extension			
Negative	81/599	13.5	0.0001
Positive	19/44	43.2	
Capillary/lymphatic space involvement			
Negative	30/366	8.2	0.0001
Positive	70/276	25.4	

found to contain tumor in stage I and IIA cases, to 57.1% when the para-aortic nodes were invaded, and to 73.7% when both nodal areas were invaded [9]. In the Memorial Sloan-Kettering Cancer Center experience [5], when recurrences did not include positive nodes, salvage could be achieved in 18% (10/56), but when recurrent carcinoma and positive nodes were both present, none of 29 patients could be salvaged.

At the MD Anderson Hospital it was observed that after a radical hysterectomy and pelvic lymphadenectomy for stage IB cervical carcinoma, patients with pelvic node metastasis showed 45% recurrence, of which 90% appeared within 24 months. In patients with adenocarcinoma the recurrence rate was 80%, versus 22% for squamous carcinoma [12].

The impact of positive nodes on 5-year survival rates reported from the University of Miami can be observed in table 11. In the presence of positive pelvic nodes the overall corrected 5-year survival rate was 63.5%, and was lowest (18.4%) when both the pelvic and para-aortic nodes were involved.

At the Memorial Sloan-Kettering Center, nodal metastasis was associated with lower survival. A group of 295 stage IB and 136 stage IIA patients operated

Table 11. Five-year survival and nodal status in 726 patients with stage IB and IIA[1] [from 9]

Nodal status	5-year survival, %
Negative nodes	95.8
Pelvic nodes +	63.5
Para-aortic nodes +	40.8
Pelvic and para-aortic nodes +	18.4

[1] Treated mainly by surgery; hysterectomy not done if para-aortic nodes were positive or extrauterine extension found.

Table 12. Five-year survival and node status (stage IB, n = 295; stage IIA, n = 136) [from 5]

Nodal status	5-year survival, %
All patients	81.7
Negative nodes	85
Positive nodes	50
Three or more node groups	12

on there (table 12) showed 85% 5-year survival when the nodes were negative versus 50% when positive. The survival went down to 12% when 3 or more node groups were involved.

The impact of lymph node metastases on survival is more remarkable in adenocarcinomas. A report based on 125 cases of stage I adenocarcinoma stated that the 5-year survival was 82% in patients with negative nodes but only 28% in node-positive patients [13]. For both histologies, the distant metastatic rate will increase with the presence and number of positive nodes.

Treatment of Lymph Node Metastases

In surgical series lymph node excision usually accompanies treatment of the primary disease, but most series exclude patients with positive para-aortic nodes or gross disease (nodes or direct extension) outside the uterus (except for vaginal fornices). These patients, and additionally those with findings associated with a high risk of recurrence, are usually submitted to postoperative

Table 13. External radiotherapy field and limits

AP-PA	
Cephalad	Junction L4–L5
Laterally	1.5 cm lateral to bony pelvis
Caudal	4 cm beyond the most distal vaginal disease, or introitus
Lateral	
Cephalad	Same as AP-PA
Anterior	Symphysis pubis
Posterior	S3 – with margin of 3–4 cm posterior to tumor
Caudal	Same as AP-PA

radiotherapy. Poorly differentiated tumors, presence of lymph node metastases, tumor at the edge of resection, deep cervical invasion, endometrial extension of tumors, and parametrial infiltration are all indications for post-operative irradiation. Some reports conclude that post-operative radiotherapy is of value [12] whereas others question its value [14]. Some feel that if radiotherapy is anticipated, completion of hysterectomy when pelvic lymph node involvement is found is not justified, as this approach does not improve results [15].

Lymphadenectomy should be for staging and should not be considered a therapeutic procedure; extending the procedure does not improve survival [16].

Pelvic radiotherapy of carcinoma of the cervix encompasses the primary tumor, its direct extensions and potentially involved nodes in the irradiated volume. The usual radiation field placement employed in patients with stage IB or higher extent is shown in table 13. Nodes in the lateral pelvic wall area will receive doses in the neighborhood of 5,500–6,000 cGy, whereas those in the paracervical region will receive doses near to, or in excess of, 8,000 cGy. Details of radiotherapy have been published [17, 18].

The results of treatment of the pelvic lymph node metastases by radiotherapy cannot be separated from those obtained from the treatment of the primary tumor, as both are treated simultaneously. Preirradiation transabdominal surgical evaluation of the lymph nodes introduces conditions not present in a virgin case; complications may be increased. Tumor control in the pelvis by radiotherapy is shown in table 14. This ranges from 91 to 98% 5-year control in stage IB to 25 to 34% in stage IV.

Irradiation doses commonly employed for treatment of the pelvis are shown in table 15. The minimal dose to the para-aortic area is 4,500 cGy with five weekly fractions of 180 cGy each. If specific metastatic masses are found,

Table 14. Pelvic tumor control [from 17; collated series]

Stage	5-year tumor control, %
IA	100
IB	91–98
IIA	84–94
IIB	75–82
III	49–64
IVA	25–34

Table 15. Doses of radiations to the pelvis used in the treatment of cancer of the cervix (all doses given in Gy)

Intracavitary brachytherapy[1] (number of insertions)		External, pelvis[2] (dose/fraction)	Total paracentral[1]
80	(2)	–	80
40	(1)	45 (1.5–1.8)	85
35	(1)	49.5–51 (1.5–1.8)	85
30	(1)	50 split: 25 (2.5) 2-week rest 25 (2.5)	80
–	–	70: 50 pelvis+20 boost	70

[1] Calculated at point A. When a tandem only is used the dose is calculated at 2 cm lateral to its center.
[2] Central axis dose at midpelvis.

Table 16. Survival with positive para-aortic nodes

Reference	Patients, n	5-year survival, %
Lovecchio et al. [19]	31	50
Potisch et al. [20]	81[1]	40
Potczaski et al. [21]	33	31

[1] Based on clinical staging.

Table 17. Prophylactic para-aortic node radiotherapy (RTOG 79–20) in 335 evaluable patients [from 22]

Area irradiated	5-year survival, %		Distant metastases alone or with pelvis as first failure, %		Presence of tumor in patients dead at 2 years, %
Pelvis and para-aortic	66	$p = 0.043$	12	$p = 0.04$	74
Pelvis only	55		22		95

and marked with silver clips, this area can be boosted to a dose as high as 6,000 cGy. The results of para-aortic node irradiation in terms of 5-year survival are shown in table 16, and range from 31 to 50%. However, 5-year survival does not mean final recurrence-free status: at the University of Miami only 20% remained free of disease though the reported 5-year actuarial survival was 50% [9].

Prophylactic Irradiation of Para-Aortic Node Area

Elective or prophylactic irradiation of the para-aortic lymph node area, to prevent the clinical manifestation of tumor in that region, has been practiced in some centers for years, but its true merit had not been proven until recently with the results of the prospective phase III study of the Radiation Therapy Oncology Group (RTOG). The study [22] analyzed 335 evaluable patients randomly assigned to pelvic only or pelvic and para-aortic irradiation. Included were cases without clinical evidence of para-aortic nodal involvement that had stage IIB disease (245 patients), or stages IB or IIA with primary tumors measuring ≥ 4 cm in lateral dimension (90 patients). Supplementing pelvic external therapy and brachytherapy, para-aortic irradiation delivered a maximum of 3,000 cGy by opposing anterior-posterior fields and an additional 1,500 cGy by lateral arc rotation, lateral shaped, or posterior oblique fields. The 5-year survival (table 17), absence of tumor in patients dead at 2 years, and freedom from distant metastasis alone or with pelvis as first site of failure were all improved with prophylactic para-aortic node irradiation.

Conclusions

Lymph node metastasis constitutes a very important prognostic factor in carcinoma of the cervix that is closely related to the site of tumor, depth and extent of invasion, degree of tumor differentiation and lymphatic space involvement.

The evaluation of nodes by surgical technique permits the most precise information but may result in complications when subsequent radiotherapy is applied. The extraperitoneal approach should result in lesser complications than transperitoneal surgery. Imaging procedures can be non-invasive or of lesser invasiveness than surgery, but are less accurate. Lymphangiogram will provide the most useful information on the status of the lymph nodes visualized, but will not show all of the nodes inside the pelvis. The use of the available imaging techniques with biopsy by needle aspiration of the suspicious nodes, together with laparoscopic node evaluation, may improve the chances of detecting and diagnosing lymph node metastasis without surgical exploration.

The average incidence of pelvic node metastasis is 16% for stage IB tumors, but will be 20.9% in gross lesions and 43% in cases with parametrial invasion in the surgical specimen (table 7). Para-aortic lymph node metastases will be present on average in 6% of stage IB, 13% of IIA, 19% of IIB, and 29% of IIIB cases, and also in 35% of barrel-shaped lesions (table 9). Patients with para-aortic node metastases will show at least a 25% incidence of scalene node metastasis. This area should always be biopsied prior to embarking on therapeutic irradiation of the para-aortic area.

The effectiveness of irradiation of pelvic node metastasis can be judged from available surgical information which permits us to estimate over 20% incidence of pelvic node metastasis in stage IB tumors submitted to irradiation, but a pelvic failure rate of radiotherapy of less than 10% (table 14). Consequently, pelvic irradiation rather than intracavitary therapy alone should be the treatment of choice of all stage IB or higher lesions.

Histologically proven para-aortic node metastasis with no scalene node involvement should have therapeutic irradiation as it may result in 5-year survival in the range of 30–50%. Prophylactic para-aortic node irradiation has shown its value in bulky stage I and more advanced tumors with no clinically evident para-aortic node metastases (based on imaging techniques): the incidence of distant metastasis, the control of tumor in the pelvis and the 5-year survival can be improved. The value of para-aortic prophylactic irradiation in patients submitted to meticulous preirradiation evaluation of nodes is being further investigated by the RTOG with a comparison of combination of pelvic irradiation and concurrent chemotherapy versus pelvic and para-aortic irradia-

tion. At this time, chemotherapy does not form part of the standard therapy in carcinoma of the cervix.

Invasive carcinoma of the cervix is a preventable, detectable and easily diagnosable disease, which has gone down in incidence and mortality in the last 30 years, but still persists with significant magnitude in cancer morbidity tables. The incremental increase of readily available public health measures should afford further reduction in the incidence and mortality from this disease, a diminution in the number of advanced tumors and a lesser metastatic lymph node problem.

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Vulvar Carcinoma: Radiotherapy or Surgery for the Lymphatics?

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Lymphatic Drainage of the Vulva

The primary lymphatic drainage of the vulva and distal vagina is to the superficial femoral (or inguinal) nodes that lie along the femoral vein [6]. Specifically, the superficial external pudendal vein nodes drain the vulva, the distal third of the vagina, the perineum, and the perianal region. This region is drained by a network of lymphatic anastomoses with frequent extension across the midline. Afferent vessels from the anterior portion of the external genitalia as well as the lower abdominal wall also extend to the superficial epigastric vein nodes in the anterior abdominal wall just above the symphysis. Efferent vessels from the superficial inguinal nodes drain to the deep inguinal and external iliac nodes. Deeper lymphatic vessels from the region of the clitoris may drain directly to the deep femoral nodes (Cloquet's node) or through the inguinal canal to the external iliac nodes. However, in practice, metastases are rarely found in the deep inguinal or pelvic nodes without evidence of spread to the superficial inguinal nodes.

Although prior to 1989 regional nodes were evaluated by clinical examination in the FIGO/AJC staging system, the accuracy of clinical assessment of the inguinal nodes is poor. This was born out in a review of 272 patients with superficial vulvar cancer who underwent inguinal node dissection: 16.5% of those with clinically negative groins had positive nodes at surgery and 40% with clinically positive groins had no histological evidence of regional metastasis [8]; only 30% of patients with regional metastases (17/57) had had clinically suspicious nodes. Computed tomography (CT) and magnetic resonance imaging may be helpful, particularly in evaluating obese patients, but only if

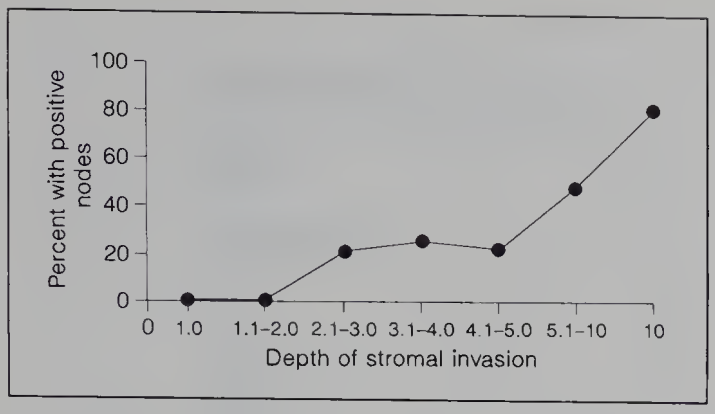

Fig. 1. The relationship between depth of stromal invasion of the primary vulvar lesion and the incidence of inguinofemoral lymph node involvement [11].

nodes are >2 cm. Fine needle aspiration of suspicious nodes may also yield useful information. However, surgical evaluation of the inguinal nodes yields the most accurate prognostic information.

Features Associated with Regional Metastases of Vulvar Neoplasms

Various authors report the incidence of positive nodes in operable vulvar cancer to be between 20 and 35%. A number of features have been correlated with the incidence of regional node metastasis: clinical stage, depth of invasion, tumor diameter, tumor thickness, lymph-vascular space invasion, keratin, mitotic activity, histologic grade, and cell type [1]. Adverse clinical and histologic features tend to be associated with one another.

Tumor diameter, in particular, correlates positively with regional metastasis. Hacker et al. [2] found positive nodes in only 4% of patients with lesions <1 cm in diameter and in 18% of patients with 1–2 cm lesions [2]. However, the incidence of positive nodes increased rapidly with increasing lesion size: 33% of patients with 3–4 cm lesions and 53% of patients with tumors >4 cm in diameter had positive nodes. The 1988 clinical FIGO staging system, which incorporated tumor size and clinical suspicion of nodal involvement, was strongly correlated with nodal involvement; approximately 25% of patients with stage II disease and 70% of patients with stage III disease have positive nodes [2].

Histologic findings in the primary specimen can be particularly helpful in predicting lymph node metastasis. Depth of invasion strongly correlates with regional spread [1] (fig. 1) as does tumor thickness. Patients with tumors that invade >10 mm have an approximately 80% risk of regional disease. Furthermore, the presence of lymph-vascular space invasion dramatically increases the

Table 1. Vulvar cancer – influence of nodal status and tumor diameter on survival [5]

Tumor diameter	Incidence of inguinal node involvement %	Five-year survival	
		negative nodes, %	positive nodes, %
≤2 cm	19	98	79
2.1–3 cm	31	91	59
3.1–4 cm	54	76	57
>4 cm	48	82	45

risk of regional metastases; Binder et al. [1] found positive nodes in 80% of patients with this finding and Sedlis et al. [8] reported 2 or more positive nodes in 40%.

Relationship between Regional Involvement and Survival

Survival is strongly correlated with the presence, number, and location of regional metastases. The survival rate for patients with more than two positive femoral nodes is <30% [2, 5]. Bilateral node involvement is associated with a particularly poor prognosis as is pelvic node involvement. In a Gynecologic Oncology Group (GOG) study involving pelvic node dissection, Homesley et al. [4] reported a 23% survival rate (at 2 years) in patients with positive pelvic nodes compared with 73% in patients without pelvic node involvement. In combination, information about tumor size and nodal status are highly predictive of prognosis [5] (table 1).

Role of Postoperative Radiation in Patients with Positive Nodes

In 1986, the GOG published the results of a prospective randomized trial that documented the important role of radiotherapy in the treatment of regionally advanced vulvar carcinoma [4]. Women who underwent radical vulvectomy and inguinal node dissection for carcinoma and who had histologically positive nodes were randomly allocated to receive either postoperative radiotherapy to the bilateral inguinal and pelvic nodes or pelvic lymph node resection. Patients were treated with anterior and posterior opposed photon fields. The study was closed prematurely when it became apparent that patients

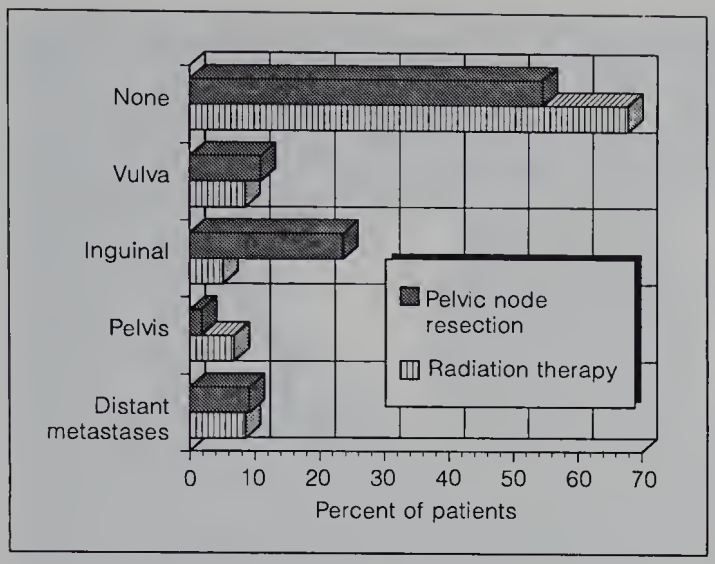

Fig. 2. Recurrence sites in patients treated on the GOG randomized trial comparing pelvic node resection with radiation therapy to the pelvis and inguinal regions. The vulva, which was treated with radical vulvectomy, was shielded [4].

treated with radiotherapy had a significantly better survival rate than those treated surgically (68 vs. 54% at 2 years). Patients with two or more positive nodes benefitted the most, with 63% surviving 2 years in the radiation therapy arm versus 37% in the pelvic node dissection arm. Patients with *clinically* positive nodes also had a better survival rate with irradiation than with pelvic dissection (63 vs. 37%). The authors commented that the follow-up was too short and the number of patients too few to accurately evaluate the value of irradiation in patients with a single microscopically positive node. Evaluation of the failure patterns revealed a significantly lower incidence of groin (inguinal) recurrences in patients who received irradiation to the groin (fig. 2). Patients whose tumors recurred in the groin usually died of their disease.

Adjuvant Groin Irradiation in Patients with Clinically Negative Nodes

Although reports of the use of radiotherapy alone to treat clinically negative nodes in high-risk patients were largely anecdotal [3, 9], most radiotherapists assumed until recently that radiation doses of 45–50 Gy could control microscopic nodal disease as efficiently in this setting as it does in many others. The improved survival of patients who received postoperative irradiation confirmed the effectiveness of radiotherapy in treating microscopic regional disease, and prompted the GOG to conduct a randomized comparison

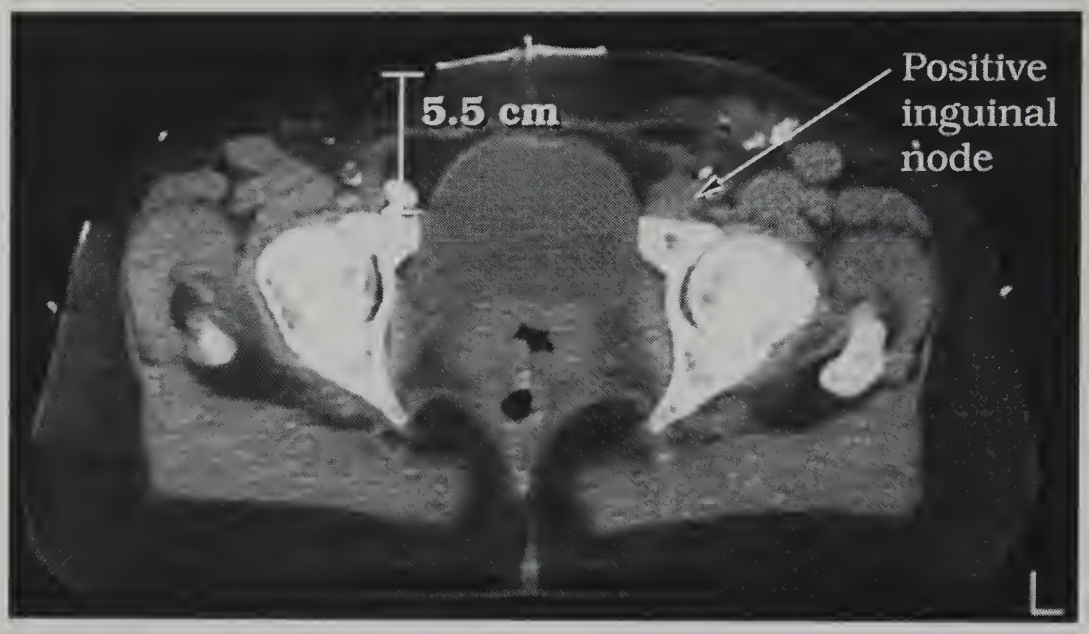

Fig. 3. A transverse CT slice through the deep femoral nodes of a 48-year-old woman with squamous carcinoma of the left labium metastatic to superficial and deep inguinal nodes. The patient was 1.7 m tall and weighed 77 kg (Quetlet index = 26). Brightly opacified nodes are from a lymphangiogram done before the CT. On the uninvolved side, the node corresponding to the positive node on the left is 5.5 cm beneath the skin surface.

between radiotherapy and the more traditional surgical treatment of clinically negative inguinal nodes [11]. In the study, patients with T1-T3 vulvar squamous carcinoma and clinically negative nodes were randomly allocated to receive inguinal node dissection or regional irradiation. The original accrual goal was 400 patients, but the study was closed after only 52 entries when the radiation arm was found to have a significantly greater number of groin recurrences than the surgery arm. In fact, the number of recurrences in the radiation arm [5] was equal to the number of patients with positive inguinal nodes in the surgery arm.

These results seem to raise serious questions about the efficacy of irradiation in this setting. However, the radiation techniques used in the GOG study may not have adequately covered the nodal areas at risk for metastatic disease. Patients were treated with anterior en face fields prescribed at a depth of 3 cm, and the protocol recommended that 50% of the dose be delivered with 12-MeV electrons. This technique delivers an inadequate dose to the superficial inguinal nodes in all but the thinnest patients and will almost always underdose the deep femoral nodes. For example, figure 3 illustrates a single CT slice from a relatively slender patient with a left vulvar lesion metastatic to superficial and deep left inguinal nodes. On the contralateral uninvolved side the correspond-

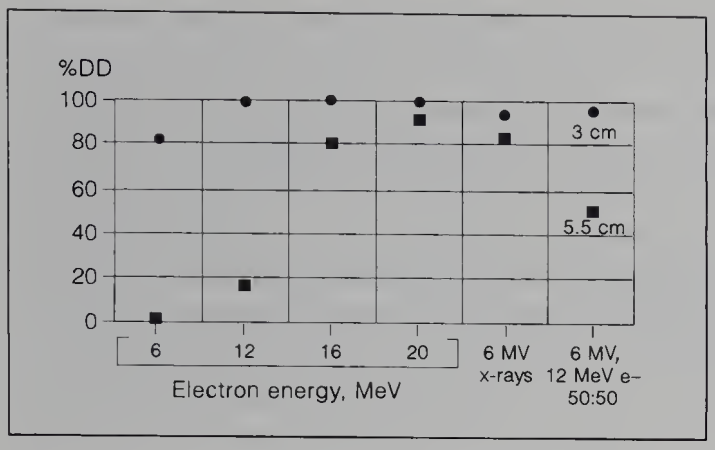

Fig. 4. Percent depth doses delivered at 3 cm and at 5.5 cm from a 10 × 10 cm appositional field composed of various energy electrons, 6-MV photons, or a mixed beam of 12-MeV electrons and 6-MV photons.

ing deep inguinal node is 5.5 cm from the surface of the patient. If this patient were treated with a 50:50 mix of 12-MeV electrons and 6-MV photons prescribed to a point 3 cm from the surface, the deep inguinal nodes would receive approximately 50% of the prescribed dose (fig. 4). The superficial inguinal nodes (which were 4.2 cm from the surface) would also be underdosed. In very obese patients, the inguinal nodes may be located 8 cm or more beneath the surface of the patient. The convention of prescribing inguinal node fields at a depth of 3 cm was developed many years ago, before the advent of CT tomography and before the widespread use of electron beam fields. The use of such an arbitrary prescription point is inappropriate when patients are treated with single anterior en face fields, particularly when electron beams are used.

Another prospective GOG study published in 1992 by Stehman et al. [10] hints at the importance of the deep femoral nodes in vulvar carcinoma. In that study, 122 patients with early vulvar carcinomas (all <2 cm in diameter) were observed after treatment with hemivulvectomy and superficial node dissection. All patients with tumors having >5 mm invasion, positive lymph nodes, or lymph-vascular space invasion in the primary lesion were excluded. Despite the favorable characteristics of this group of patients, the investigators observed 9 groin recurrences in 122 patients. Six of these recurrences were in the ipsilateral dissected groin. The authors speculated that, contrary to conventional wisdom, the deep femoral nodes sometimes harbor disease even when the superficial inguinal nodes are negative.

In a recent study that attempted to address the confusion generated by these studies. Petereit et al. [7] retrospectively reviewed the University of Wisconsin experience with radiotherapeutic management of clinically negative

inguinal nodes. Twenty-four patients who were treated with radical vulvectomy and bilateral node dissection were compared with 18 patients who underwent radical vulvectomy and inguinofemoral node irradiation. Patients were treated with anterior and posterior opposed photon fields weighted to favor the anterior. Although the radiation-treated patients included a greater percentage of unfavorable T3 and T4 lesions (33 vs. 4%) there was no difference in the incidence of inguinal node failures (one in the surgery group and two in the radiation group; $p = 0.56$). The morbidity of node dissection was considerable, with grade 2–3 wound separation in 37%, infection in 46%, and lymphedema in 12%. Radiation complications included mild acute skin reaction in 45% and lymphedema in 1 patient. The authors concluded that patients with clinically negative inguinal nodes were effectively treated with irradiation alone if radiation techniques were used that adequately encompassed the inguinofemoral nodes.

Conclusions

Three conclusions can be drawn from the above-mentioned data. First, patients with multiple positive nodes or gross inguinal nodal disease at node dissection benefit from postoperative inguinal irradiation. Second, occult inguinal metastases probably can be controlled with radiotherapy with less morbidity with than that occasioned by surgery if the superficial and deep inguinal nodes are adequately covered. However, the effectiveness of radiotherapy in this setting continues to be controversial. Finally, the depth of inguinal nodes should always be verified with radiographic imaging (e.g. CT) if electrons are used in the treatment plan.

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Management of the Regional Lymph Nodes in Malignant Melanoma: Surgery, Radiotherapy or Observation

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The regional lymph node is the most common site of melanoma metastasis. Increasing tumor burden within the regional nodes is associated with decreasing survival, as shown for patients who have no metastases to regional lymph nodes compared with those with microscopic or clinically evident disease, and also for patients with micrometastases to lymph nodes compared with those with clinically palpable disease. For patients presenting with high-risk primary disease, there are no known systemic adjuvant agents that effectively reduce the risk of later distant disease. Therefore, treatment of the regional lymphatics as potential sources of dissemination is a major focus of clinical investigation and a pertinent topic for this volume.

As a surgical intervention for regional lymphatic disease, a lymphadenectomy can be undertaken as *therapeutic* for patients with clinically palpable or histologically proven metastases, or *elective* for patients with a relatively higher risk for harboring occult lymph node metastases based upon analysis of the primary lesion. Whenever we try to apply an invasive treatment modality to patients with cancer, the foremost goal must be improving the chance of cure. Improved staging and local-regional control of disease may also be beneficial. These goals must be balanced against concerns regarding cosmesis, surgical complications, and cost.

The Role of Therapeutic Lymph Node Dissections

Prognostic risk factors for the development of distant metastases, identified in patients with positive regional lymph nodes (stage III disease), include: the number of lymph nodes involved, the presence or absence of extracapsular extension, and the thickness and presence of ulceration of the primary tumor. By far the most important of these is the number of lymph nodes involved, showing that increasing tumor burden within the regional basin portends poorer prognosis.

The rationale for performing a complete lymphadenectomy for patients with proven nodal metastases is that 60–75% of patients with palpable nodal metastases have other nodes involved within the same nodal basin. In the absence of any proven effective adjuvant systemic therapy, an incomplete node dissection may risk the chance for cure and regional control of disease. With the availability of fine needle aspiration, it is advisable to confirm that the patient has histologic disease before embarking on a radical operation: approximately 30% of clinically abnormal nodes are not involved with malignancy histologically.

Inguinal Region

The morbidity of lymph node dissection may be greater in the inguinal area than in other sites such as the axilla, particularly if a deep node dissection is included with the superficial. This was traditionally done if there were clinically positive nodes superficially. However, patients with positive nodes in the deep system have such poor prognosis that this procedure has been questioned, especially in view of its increased morbidity.

Studies at Memorial Sloan-Kettering Cancer Center have identified prognostic factors for deep node involvement [1]. An important one is the presence of more than three positive nodes within the superficial basin. In addition, when Cloquet's node (which intervenes between the superficial and the deep nodal basins) is positive, it is predictive of deep nodal disease in almost 80% of cases. Conversely, when it is negative, only 3% of patients have deep nodal involvement. As a result, dissections are now often limited to the superficial femoral triangle when Cloquet's node is found to be negative.

Head and Neck Region

Traditionally the radical neck dissection was the treatment of choice for patients who had palpable disease in this region. In spite of this radical operation, which includes removal of the sternocleidomastoid muscle, the internal jugular vein and the eleventh cranial nerve, the recurrence rates in the dissected basin were high. Our head and neck surgeons at M.D. Anderson have

championed the functional neck dissection approach, which spares these anatomic structures, and have used adjuvant irradiation for optimizing local control [2]. Their experience to date shows that there have been improvements in local control, cosmesis and physiologic function.

The Potential Role of Elective Lymph Node Dissections

The use of elective lymph node dissection (ELND) is controversial because the clinical results reported in the literature are conflicting. A number of studies support ELND, but are retrospective, nonrandomized reviews. The two prospective randomized trials with sufficient duration of clinical follow-up for analysis do not demonstrate a survival benefit of ELND. However, these trials were undertaken before the relevant prognostic factors were clearly defined, and probably did not target appropriate patient populations for treatment.

Retrospective Studies

It seems reasonable to expect that a lymphadenectomy would be of greater benefit – for survival or regional control – when the involvement is microscopically limited within the nodes (often to the subcapsular sinusoids), as compared with delaying the node dissection until the nodes are palpable (often completely replaced by melanoma). Retrospective, nonrandomized trials from the Sydney Melanoma Unit, University of Alabama, Pack Medical Group, Memorial Sloan-Kettering Cancer Center and Duke University evaluated the results of ELND and showed a survival benefit of ELND [3–5]. Results from the University of Pennsylvania did not. These analyses are limited because they report trials with potentially uncontrolled selection of patients for treatment, but they do suggest patient groups most likely to benefit from ELND. The largest series reported data combined from the University of Alabama and the Sydney Melanoma Unit [4]. There was no survival benefit in patients with thin melanomas, as their risk of failure was low (table 1). Also, there was no survival benefit for thicker melanomas, as their risk for distant disease was excessively high. Clearly, it is the intermediate thickness group of patients that may benefit from ELND.

Prospective Studies

There have been four prospective randomized trials. The first two were performed before most of the retrospective studies were published, which have defined the patient populations that may benefit from ELND, and prior to other studies that have given insight into the important prognostic factors of the primary such as tumor thickness and ulceration. The other two studies have

Table 1. Ten-year survival rates of clinical stages I and II melanoma treated at the Sydney Melanoma Unit and University of Alabama at Birmingham [modified from 3]

Tumor thickness, mm	Ten-year survival rates				p value
	WLE only		WLE + RND		
	%	n	%	n	
Melanomas of the extremities					
<0.76	94	142	100	26	0.230
0.76–1.49	74	125	92	66	0.042
1.50–3.99	54	114	80	107	0.005
≥4.00	30	33	44	34	0.400
Melanomas of the trunk, and head and neck					
<0.76	96	135	83	38	0.343
0.76–1.49	56	131	80	51	0.049
1.50–3.99	33	129	64	129	0.0008
≥4.00	22	56	26	38	0.806

WLE = Wide local excision; RND = regional node dissection.

completed accrual, but follow-up is not sufficient to provide any insight into their results.

The WHO trial was initiated in 1969, and randomized patients to receive a wide local excision alone versus wide local excision plus ELND [6]. Patients who developed nodal disease in the observation arm had a delayed lymph node dissection. Although this study did not show any survival benefit to ELND, there were significant limitations in its design. For instance, 85% of the study group patients were females with thin distal extremity lesions; these are now known to be a highly favorable group and are unlikely to need ELND. Any possible benefits of ELND afforded to the higher risk groups would likely be obscured, because they constituted a small proportion of the total patient population. When a separate analysis was done of patients that were in a higher risk group, that is, the intermediate thickness melanomas, there was a trend toward an improved survival rate after ELND.

The smaller Mayo Clinic study was a randomization between three treatment arms: wide local excision alone, wide local excision plus ELND, or ELND delayed 30–60 days after wide local excision (with the intent to catch more in-transit disease as it traveled from the primary lesion to the nodal basin) [7]. Unfortunately, only 7 of the 110 patients (6%) who underwent ELND had positive nodes, indicating that these patient groups were also in a highly favorable group. In the experience of most investigators, elective node dissec-

tion for appropriately selected patients results in at least a 20–25% incidence of occult positivity.

More recently, the WHO established a randomized trial for trunk melanomas greater than 1.5 mm in tumor thickness. Also, the Intergroup Melanoma Study has completed patient accrual for a protocol evaluating just the intermediate thickness group of patients. All anatomic sites were treated in this trial, with primary lesions 1.0–4.0 mm in tumor thickness. Patients were randomized between wide local excision and observation, and wide excision plus ELND. The appropriate nodal basins at risk were identified by preoperative lymphoscintigraphy, and if two nodal basins were identified for trunk lesions, both were dissected. 800 patients have been enrolled, but the results will not be clear until adequate follow-up time is achieved – likely 8 years or longer.

The potential morbidities of ELND include seroma, infection, and wound edge necrosis; these are generally short-term complications with no long-term impact. The incidence of these is low in the axilla and in the neck, but higher in the inguinal area. Lymphedema, particularly in the lower extremities, is the most important long-term complication; some studies show that moderate to severe lymphedema may occur in the lower extremity in up to 15–20% of cases. Appropriate selection of patients should minimize this morbidity by considering the known risk factors for complications from lymphadenectomy – older age, obesity, or significant smoking history.

While the results of the randomized trials will improve our understanding of the role of ELND, we currently understand that patients with primary melanoma lesions of thickness from 1.0 to 4.0 mm carry a regional risk of disease of 25–45%, but a significantly lower risk of distant disease of 10–20%. This group may likely benefit from ELND, which provides expectant palliation for a large percentage of patients, provides accurate staging, treats metastases earlier in the course of the disease, and may improve survival.

Lymphatic Mapping for Lymphadenectomy Planning

Lymphoscintigraphy

Lymphoscintigraphy uses radioactive colloid to identify routes of lymphatic drainage [see Kaplan, this volume]. For many primary sites, these routes are far more ambiguous anatomically than previously thought. If this study is indicated, it is important to perform it prior to the wide local excision; afterward, the skin that is left may not represent the lymphatic drainage of the primary melanoma. If the pattern of drainage involves two nodal basins, then it may be reasonable to carry out elective nodal dissections of both.

Lymphoscintigraphy may help us increase the identification not only of the nodal basins at risk in ambiguous drainage areas, but also of the location of the sentinel node within a nodal basin. This may allow us to make incisions smaller and more strategically placed in terms of finding the sentinel node, as described below.

Sentinel Node Biopsy

A rational approach would be to provide node dissections only for patients with proven micrometastases – an approach that could satisfy both the advocates and opponents of ELND. Toward this goal, a procedure that uses selective lymphadenectomy with intraoperative lymphatic mapping and sentinel node biopsy was reported by Morton et al. [8].

In theory, this procedure accurately identifies patients with nodal metastases. It is believed that the lymphatic drainage of finite areas of skin is directed initially to a specific node within a nodal basin, the so-called sentinel node. An intradermal injection of a vital blue dye into the melanoma site can identify this sentinel node for removal and histologic examination. This could permit accurate staging of a nodal basin, and allow selective use of regional node dissections for patients with sentinel nodes positive for involvement.

Candidates for lymphatic mapping might include stage I or II patients with intermediate thickness melanomas, for potential cure and improved staging, and those with thicker lesions, for better staging and expectant palliation. Again, patients who have already received a formal wide excision are not candidates because the skin that is now remaining may not accurately reflect the lymphatic drainage of the primary melanoma.

Morton et al. [8] have evaluated this technique in patients with stage I and II disease and with tumors 0.65–4.0 mm in thickness, and have mapped 237 nodal basins. Lymphadenectomy was peformed in addition to intraoperative lymphatic mapping and sentinel node biopsy. They were able to identify the sentinel node in 82% of cases. Of these, 40 (21%) had positive nodes on dissection – including the sentinel node in 38/40. Therefore, the false negative rate was only 5%.

We have embarked on a confirmation study for patients with stage I and II melanomas of intermediate thickness; the study centers currently include the M.D. Anderson Cancer Center and the University of South Florida in Tampa. This study has evaluated the sentinel node identification rate according to the nodal basin site, the percentage of sentinel nodes with metastases, and the false negative rate. The results in 54 nodal basins mapped so far are shown in table 2. In 8 of 12 patients with occult metastases, the sentinel node was the only positive node. In the other 4, in addition to the sentinel node there were only 1 or 2 other nodes that were positive – suggesting that we were identifying disease

Table 3. The role of adjuvant irradiation

Rationale for adjuvant radiotherapy
Surgery alone does not provide effective regional control for a subgroup of patients
Groups identified to be at high risk for recurrence have a >30% risk of failure in the surgical bed after therapeutic lymphadenectomy
Local-regional control is an important issue in terms of expectant palliation and quality of life
Patients at high risk (>30%) for recurrence following lymphadenectomy
Four or more positive nodes
Matted nodes
Extracapsular extension of disease
Recurrence in the nodal basin after prior dissection

primary site to the regional nodes. The purpose was to try to spare patients the morbidity of an elective neck dissection, or to reduce the regional recurrence rates after therapeutic dissection.

Three groups of patients have been treated: new primary melanomas ≥ 1.5 mm and with NO disease; new primary lesions with synchronous regional lymphadenopathy, and previously controlled primary lesions with new nodal metastases. In the second and third groups, irradiation has followed node dissection. The radiotherapy was generally hypofractionated: 6 Gy/fraction, twice per week, for 5 fractions total (30 Gy). The results show that in all groups the local-regional control has been excellent, with a local-regional control rate of approximately 95% [2].

Axillary Region

We have evaluated our experience with axillary irradiation following lymphadenectomy for metastatic melanoma (table 4). Twenty-eight patients received postoperative irradiation to the axilla; 21 were treated adjuctively and 7 for gross residual disease. All patients had undergone a formal axillary node dissection; some had multiple dissections, and in some the dissections went into the supraclavicular fossa. All patients had either extracapsular disease, multiple nodes involved, or recurrence of disease in a previously dissected basin. Twenty-two of 28 were irradiated using hypofractionated regimens. Over the mean follow-up period of 56 months, 16 of the 21 patients have remained in control in the dissected basin for a control rate of 71%.

We feel that the acute and late effects of regional nodal irradiation for malignant melanoma appear acceptable. There is a remarkably low local recurrence rate for these high-risk patients treated for subclinical disease. A clinical trial is required to assess the appropriateness of routine irradiation for high-risk patients.

Table 4. Adjuvant irradiation following axillary lymphadenectomy for metastatic melanoma

	Treated		Recurred	
	n	%	n	%
Extent of disease				
Gross residual	7		5	71
Microscopic	21		1	5
Complications				
Arm edema	5	18		
Functional impairment	0	0		

Note: All patients were irradiated using a hypofractionated scheme.

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We are entering a new era of understanding the lymphatic system brought about by important insights from experimental investigations and clinical trials.
To achieve a cure, cancer therapies (whether by surgery, radiotherapy or systemic means) must be directed against the routes of cancer spread. The management of the regional lymphatics/lymph nodes, often the first site of involvement, is frequently a key decision in defining modern treatment programs. Important new insights now challenge the basis of traditional cancer therapy recommendations.
This volume brings together foremost authorities to outline the latest results in the management of the lymphatic system in cancer. Aggressive therapy or no treatment? Radiotherapy, surgery or systemic therapy? Combined modality or single modality therapy? For all major cancers – head and neck, lung, breast, gastrointestinal, genitourinary, gynecologic – current controversies are highlighted and specific recommendations for clinical treatment programs are clearly defined.

Cover illustration: Structure of a normal human lymph node by F

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